

1H-PYRAZOLE AND 1H-PYRROLE-AZABICYCLIC COMPOUNDS FOR THE TREATMENT OF DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of US provisional application Serial No. 60/400,339 filed on 08/01/2002, under 35 USC 119(e)(i), which is incorporated herein by reference in its entirety.

FIELD OF INVENTION

10 Nicotinic acetylcholine receptors (nAChRs) play a large role in central nervous system (CNS) activity. Particularly, they are known to be involved in cognition, learning, mood, emotion, and neuroprotection. There are several types of nicotinic acetylcholine receptors, and each one appears to have a different role in regulating CNS function. Nicotine affects all such receptors, and has a variety of activities.
15 Unfortunately, not all of the activities are desirable. In fact, one of the least desirable properties of nicotine is its addictive nature and the low ratio between efficacy and safety. The present invention relates to molecules that have a greater effect upon the $\alpha 7$ nAChRs as compared to other closely related members of this large ligand-gated receptor family. Thus, the invention provides compounds that are active drug
20 molecules with fewer side effects.

 The invention also concerns the synthesis of and isolation of intermediates and final compounds. Specifically, the present invention concerns the preparation of 1*H*-pyrazole and 1*H*-pyrrole-azabicyclic compounds and pharmaceutically acceptable salts thereof.

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BACKGROUND OF THE INVENTION

 US Patent 6,255,490 discloses 7-azabicyclo[2.2.1]-heptane and -heptene derivatives as cholinergic receptor ligands.

 US Patent 6,117,889 discloses 7-azabicyclo[2.2.1]-heptane and -
30 heptene derivatives as analgesics and anti-inflammatory agents.

 US Patent 6,060,473 discloses 7-azabicyclo[2.2.1]-heptane and -heptene derivatives as cholinergic receptor ligands.

US Patent 6,054,464 discloses azabicyclic esters of carbamic acids useful in therapy, especially in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, as well as intermediates and use of intermediates in synthesis.

5 US Patent 5,977,144 discloses compositions for benzyldiene- and cinnamylidene-anabaseines and methods for using these compositions for treating conditions associated with defects or malfunctioning of nicotinic subtypes brain receptors. These compositions target the $\alpha 7$ receptor subtype with little or no activation of the $\alpha 4\beta 2$ or other receptor subtypes.

10 US Patent 5,712,270 discloses a group of 2-aroylaminothiazole derivatives which bind to and stimulate central muscarinic acetylcholine receptors and are useful agents for treating symptoms of cognitive disorders, specifically the impaired memory associated with a decrease in the neurotransmitter, acetylcholine. Some of the compounds of this invention also bind to 5HT_{1A} receptors and dopamine D₂ receptors,
15 making them useful as antipsychotic agents.

US Patent 5,624,941 discloses pyrazole derivatives useful in pharmaceuticals in which cannabis is known to be involved.

US Patent 5,561,149 discloses the use of a mono or bicyclic carbocyclic, or heterocyclic carboxylic, acid ester or amide or an imidazolyl carbazol in the
20 manufacture of a medicament suitable for the treatment of stress-related psychiatric disorders, for increasing vigilance, for the treatment of rhinitis or serotonin-induced disorders and/or coadministration with another active agent to increase the bioavailability thereof, or for nasal administration.

US Patent 5,510,478 discloses a group of 2-aroylaminothiazole derivatives
25 which bind to and stimulate central muscarinic acetylcholine receptors and are useful agents for treating symptoms of cognitive disorders, specifically the impaired memory associated with a decrease in the neurotransmitter, acetylcholine. Some of the compounds of this invention also bind to 5HT_{1A} receptors and dopamine D₂ receptors, making them useful as antipsychotic agents.

30 US Patent 5,342,845 discloses indole derivatives and drugs effective as gastrointestinal motor activity regulator, antimigraine, antipsychotic or antianxiety drugs.

US Patent 5,237,066 discloses enantiomers of absolute configuration S of amide derivatives of 3-aminoquinuclidine, the process for preparing them and their use as medicinal products having activity in respect of gastric movements and antiemetic activity. US Patent 5,217,975 discloses azabicyclic compounds for
5 treating dementia.

US Patent 5,206,246 discloses anxiolytic-R-N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and thiobenzamides, their N-oxides and pharmaceutically acceptable salts thereof. A preferred compound is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.

10 US Patent 5,106,843 discloses heterocyclic compounds useful as 5-HT₃ antagonists.

US Patent 5,057,519 discloses 5-HT₃ antagonists as being useful in reducing opiate tolerance.

US Patent 5,039,680 discloses 5-HT₃ antagonists in preventing or reducing
15 dependency on dependency-inducing agents.

US Patent 5,025,022 discloses a method of treating or preventing schizophrenia and/or psychosis using S-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides, their N-oxides and pharmaceutically acceptable salts thereof. A preferred compound is S(-)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.
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US Patent 5,017,580 discloses memory enhancing R-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides, their N-oxides and pharmaceutically acceptable salts thereof. A preferred compound is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.

25 US Patent 4,988,691 discloses isoxazole-containing compounds exhibiting anti-serotonin activity.

US Patent 4,835,162 discloses agonists and antagonists to nicotine as smoking deterrents.

US Patent 4,822,795 discloses pharmaceutically useful esters and amides
30 having 5-HT₃ antagonist activity.

US Patent 4,803,199 discloses pharmaceutically useful heterocyclic acid esters and amides or alkylene bridged piperidines as serotonin M antagonists.

US Patent 4,798,829 discloses 1-azabicyclo[3.2.2]nonane derivatives having gastric motility enhancing activity and/or anti-emetic activity and/or 5-HT receptor antagonist activity.

US Patent 4,789,673 discloses dicarboxylic, heterocyclic and substituted benzoic acid alkylene-bridged piperidyl amides and esters as being serotonin M antagonists.

US Patent 4,721,720 discloses a method of treating emesis, anxiety and/or irritable bowel syndrome.

US Patent 4,657,911 discloses 3-amino quinuclidine derivatives and the application thereof as accelerators of gastro-intestinal motor function and as medicament potentiators.

US Patent 4,605,652 discloses a method of enhancing memory or correcting memory deficiency with arylamido (and arylthioamido)-azabicycloalkanes, and the pharmaceutically acceptable acid addition salts, hydrates and alcoholates thereof.

WO 01/76576 discloses a pharmaceutical composition for treatment of acute, chronic pain and/or neuropathic pain and migraines.

WO 01/60821 discloses biarylcarboxamides.

WO 01/36417 A1 discloses N-azabicyclo-amide derivatives and use in therapy, especially in the treatment of prophylaxis of psychotic disorders and intellectual impairment disorders.

WO 01/29304 discloses quinuclidine acrylamides.

WO 00/73431 A2 discloses two binding assays to directly measure the affinity and selectivity of compounds at the $\alpha 7$ nAChR and the 5-HT₃R. The combined use of these functional and binding assays may be used to identify compounds that are selective agonists of the $\alpha 7$ nAChR.

WO 92/15579 discloses multicyclic tertiary amine polyaromatic squalene synthase inhibitors and method of treatment for lowering serum cholesterol levels using the compounds.

WO 90/14347 A as abstracted in chemical abstract 1991:143,158 discloses N-quinuclidinyl-indolecarboxamide derivatives as being antiemetics.

FR 2 625 678 discloses N-(quinuclidin-3-yl)-benzamides and thiobenzamides useful as diet-control agents.

In *Bioorg. & Med.Chem. Lett.* 11 (2001) 319-321, the 5-HT₃ antagonist tropisetron (ICS 205-930) is discussed as a potent and selective $\alpha 7$ Nicotinic receptor partial agonist.

In *Behavioral Brain Res.*, 113 (2000) 169-181, it is discussed that the brain $\alpha 7$ nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease using DMXBA which is known as GTS-21.

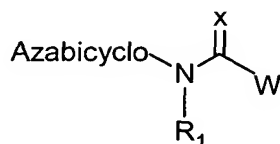
Cell surface receptors are, in general, excellent and validated drug targets. nAChRs comprise a large family of ligand-gated ion channels that control neuronal activity and brain function. These receptors have a pentameric structure. In mammals, this gene family is composed of nine alpha and four beta subunits that co-assemble to form multiple subtypes of receptors that have a distinctive pharmacology. Acetylcholine is the endogenous regulator of all of the subtypes, while nicotine non-selectively activates all nAChRs.

The $\alpha 7$ nAChR is one receptor system that has proved to be a difficult target for testing. Native $\alpha 7$ nAChR is not routinely able to be stably expressed in most mammalian cell lines (Cooper and Millar, *J. Neurochem.*, 1997, 68(5):2140-51). Another feature that makes functional assays of $\alpha 7$ nAChR challenging is that the receptor is rapidly (100 milliseconds) inactivated. This rapid inactivation greatly limits the functional assays that can be used to measure channel activity.

Recently, Eisele et al. has indicated that a chimeric receptor formed between the N-terminal ligand binding domain of the $\alpha 7$ nAChR (Eisele et al., *Nature*, 366(6454), p 479-83, 1993), and the pore forming C-terminal domain of the 5-HT₃ receptor expressed well in *Xenopus* oocytes while retaining nicotinic agonist sensitivity. Eisele et al. used the N-terminus of the avian (chick) form of the $\alpha 7$ nAChR receptor and the C-terminus of the mouse form of the 5-HT₃ gene. However, under physiological conditions the $\alpha 7$ nAChR is a calcium channel while the 5-HT₃R is a sodium and potassium channel. Indeed, Eisele et al. teaches that the chicken $\alpha 7$ nAChR/ mouse 5-HT₃R behaves quite differently than the native $\alpha 7$ nAChR with the pore element not conducting calcium but actually being blocked by calcium ions. WO 00/73431 A2 reports on assay conditions under which the 5-HT₃R can be made to conduct calcium. This assay may be used to screen for agonist activity at this receptor.

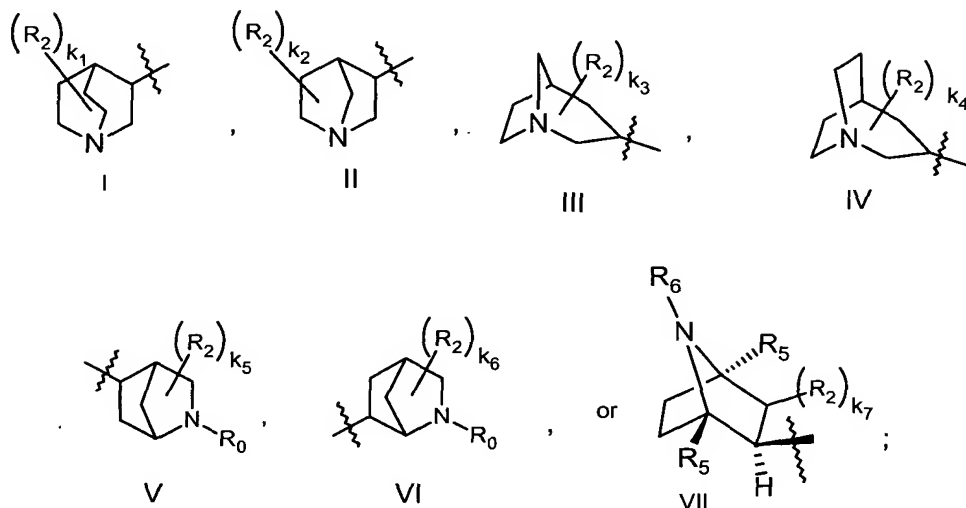
SUMMARY OF THE INVENTION

The present invention discloses compounds of the Formula I:

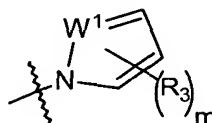


Formula I

wherein Azabicyclo is



W is



wherein W^1 is N or CH;

X is O or S;

R_0 is H, lower alkyl, substituted lower alkyl, or halogenated lower alkyl;

R_1 is H, alkyl, halogenated alkyl, cycloalkyl, substituted phenyl, or substituted naphthyl;

R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

k_1 , k_2 , k_5 , k_6 , and k_7 are independently 0, or 1;

k_3 , and k_4 are independently 0, 1, or 2;

Each R_3 is independently F, Cl, Br, I, -CN, -NO₂, alkyl, halogenated alkyl, substituted alkyl, alkenyl, halogenated alkenyl, substituted alkenyl, alkynyl,

halogenated alkynyl, substituted alkynyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, aryl, R_7 , R_9 , $-OR_{10}$, $-SR_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SCN$, $-S(O)N(R_{10})_2$, $-S(O)_2N(R_{10})_2$, $-C(O)R_{10}$, $-C(O)_2R_{10}$, $-C(O)N(R_{10})_2$,
 5 $C(R_{10})=N-OR_{10}$, $-NC(O)R_7$, $-NC(O)R_8$, $-NC(O)R_9$, $-N(R_{10})_2$, $-NR_{10}C(O)R_{10}$, $-NR_{10}S(O)_2R_{10}$, or two R_3 on adjacent carbon atoms may fuse to form a 6-membered ring to give a 5-6 fused, bicyclic moiety where the 6-membered ring is optionally substituted with 1-3 substituents selected from R_4 ;

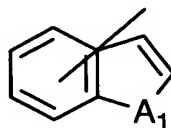
m is 0, 1, or 2;

10 R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, $-OR_8$, $-SR_8$, $-S(O)_2R_8$, $-S(O)R_8$, $-OS(O)_2R_8$, $-N(R_8)_2$, $-C(O)R_8$, $-C(S)R_8$, $-C(O)OR_8$, $-CN$, $-C(O)N(R_8)_2$, $-NR_8C(O)R_8$, $-S(O)_2N(R_8)_2$, $-NR_8S(O)_2R_8$, $-NO_2$, $-N(R_8)C(O)N(R_8)_2$, substituted alkyl, substituted alkenyl, substituted alkynyl,
 15 substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and R_{15} , naphthyl, naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or R_{15} , or two R_4 on adjacent carbon atoms may combine to form a three-ring-fused-5-6-6 system optionally substituted with up to 3 substituents independently selected from
 20 Br, Cl, F, I, $-CN$, $-NO_2$, $-CF_3$, $-N(R_8)_2$, $-N(R_8)C(O)R_8$, alkyl, alkenyl, and alkynyl;

Each R_5 is independently H, alkyl, or substituted alkyl;

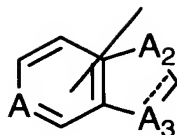
R_6 is H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, $-OH$, $-CN$, $-NH_2$, $-NH(alkyl)$, or $-N(alkyl)_2$;

R_7 is 5-membered heteroaromatic mono-cyclic moieties containing within the
 25 ring 1-3 heteroatoms independently selected from the group consisting of $-O-$, $=N-$, $-N(R_{14})-$, and $-S-$, and having 0-1 substituent selected from R_{15} , and further having 0-3 substituents independently selected from F, Cl, Br, or I, or R_7 is 9-membered fused-ring moieties having a 6-membered ring fused to a 5-membered ring and having the formula

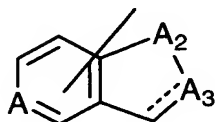


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wherein A_1 is O, S, or NR_{14} ,



wherein A is CR₁₇ or N, and each A₂ or A₃ is independently selected from CR₁₇, O, S, N, or NR₁₄, or



- 5 wherein A is CR₁₇ or N, and each A₂ or A₃ is independently selected from CR₁₇, O, S, N, or NR₁₄, and, each 9-membered fused-ring moiety having 0-1 substituent selected from R₁₅, and further having 0-3 substituent(s) independently selected from F, Cl, Br, or I, and having a bond directly or indirectly attached to the core molecule where valency allows in either the 6-membered or the 5-membered ring of the fused-ring
10 moiety;

Each R₈ is independently H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R₁₅;

- 15 R₉ is 6-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms selected from =N- and having 0-1 substituent selected from R₁₅ and 0-3 substituent(s) independently selected from F, Cl, Br, or I, or R₉ is 10-membered heteroaromatic bi-cyclic moieties containing within one or both rings 1-3 heteroatoms selected from =N-, including, but not limited to, quinolinyl or
20 isoquinolinyl, each 10-membered fused-ring moiety having 0-1 substituent selected from R₁₅, and 0-3 substituent(s) independently selected from F, Cl, Br, or I and having a bond directly or indirectly attached to the core molecule where valency allows;

- Each R₁₀ is independently H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from R₁₃, cycloalkyl substituted with 1
25 substituent selected from R₁₃, heterocycloalkyl substituted with 1 substituent selected from R₁₃, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, phenyl, or substituted phenyl;

Each R₁₁ is independently H, alkyl, cycloalkyl, heterocyclo-alkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

R_{12} is $-\text{NO}_2$, $-\text{CN}$, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, $-\text{OR}_{11}$, $-\text{SR}_{11}$, $-\text{N}(\text{R}_{11})_2$, $-\text{C}(\text{O})\text{R}_{11}$, $-\text{C}(\text{O})\text{N}(\text{R}_{11})_2$, $-\text{NR}_{11}\text{C}(\text{O})\text{R}_{11}$, $-\text{S}(\text{O})_2\text{N}(\text{R}_{11})_2$, or $-\text{NR}_{11}\text{S}(\text{O})_2\text{R}_{11}$;

5 R_{13} is $-\text{OR}_{11}$, $-\text{SR}_{11}$, $-\text{N}(\text{R}_{11})_2$, $-\text{C}(\text{O})\text{R}_{11}$, $-\text{SOR}_{11}$, $-\text{SO}_2\text{R}_{11}$, $-\text{C}(\text{O})\text{N}(\text{R}_{11})_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NR}_{11}\text{C}(\text{O})\text{R}_{11}$, $-\text{S}(\text{O})_2\text{N}(\text{R}_{11})_2$, $-\text{NR}_{11}\text{S}(\text{O})_2\text{R}_{11}$, or $-\text{NO}_2$;

R_{14} is independently H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl;

10 R_{15} is alkyl, substituted alkyl, halogenated alkyl, $-\text{OR}_{11}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}(\text{R}_{10})_2$;

R_{17} is H, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, R_{18} , $-\text{OR}_{11}$, $-\text{SR}_{11}$, $-\text{N}(\text{R}_{11})_2$, $-\text{NR}_{11}\text{S}(\text{O})_2\text{R}_{11}$, F, Cl, Br, or I, or a bond directly or indirectly attached to the core molecule, provided that there is only one said bond to the core molecule within the 9-membered fused-
15 ring moiety, further provided that the fused-ring moiety has 0-1 substituent selected from alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, R_{18} , $-\text{OR}_{11}$, $-\text{SR}_{11}$, $-\text{NR}_{11}\text{R}_{11}$, $-\text{C}(\text{O})\text{R}_{11}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{NR}_{11}\text{R}_{11}$, $-\text{CN}$, $-\text{NR}_{11}\text{C}(\text{O})\text{R}_{11}$, $-\text{S}(\text{O})_2\text{NR}_{11}\text{R}_{11}$, or $-\text{NR}_{11}\text{S}(\text{O})_2\text{R}_{11}$, and further provided that the fused-ring moiety has 0-3 substituent(s) selected from F, Cl, Br, or I;

20 R_{18} is alkyl, cycloalkyl, heterocycloalkyl, any of which is substituted with 0-3 substituents independently selected from F, Cl, Br, or I and further substituted with 1 substituent selected from $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}_{10}$, $-\text{SR}_{10}$, $-\text{NR}_{10}\text{R}_{10}$, $-\text{C}(\text{O})\text{R}_{10}$, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{10}$, $-\text{NR}_{10}\text{C}(\text{O})\text{R}_{10}$, $-\text{S}(\text{O})_2\text{NR}_{10}\text{R}_{10}$, $-\text{NR}_{10}\text{S}(\text{O})_2\text{R}_{10}$, phenyl, or phenyl having 1 substituent selected from R_{15} and further having 0-3 substituents

25 independently selected from F, Cl, Br, or I;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof.

The compounds of Formula I are used to treat any one of or combination of cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration
30 associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury,

behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post
 5 traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

10 Embodiments and aspects of the invention may include the following.

An embodiment of the present invention provides a method comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof or pharmaceutical composition containing said compound or salt thereof, to the mammal.

15 The compound of Formula I, where X is O or S.

The compound of Formula I, where any one of k_1 , k_2 , k_3 , k_4 , k_5 , k_6 , or k_7 is 1. The compound of Formula I, where any one of k_1 , k_2 , k_3 , k_4 , k_5 , k_6 , or k_7 is 0, this means R_2 is absent. The compound of Formula I, where each k_3 or k_4 is 2.

20 The compound of Formula I, where R_0 is H, lower alkyl, substituted lower alkyl, or halogenated lower alkyl, where R_1 is H, alkyl, or cycloalkyl, and where each R_2 is independently absent, alkyl, substituted alkyl, cycloalkyl, halogenated alkyl, or aryl.

The compound of Formula I, where Azabicyclo is any one or more or combination of the following: I, II, III, IV, V, VI, or VII.

25 The compound of Formula I, where each R_5 is independently H, lower alkyl, or substituted lower alkyl.

The compound of Formula I, where R_6 is an amino protecting group.

30 The compound of Formula I, where R_6 is H, or lower alkyl optionally substituted with up to 3 substituents independently selected from F, Cl, Br, I, -OH, -CN, -NH₂, -NH(alkyl), or -N(alkyl)₂.

The compound of Formula I, where at least one R_5 is H and one R_5 is H or lower alkyl optionally substituted with 1 substituent selected from -CN, -NO₂, -OR₁₀, -SR₁₀, -S(O)R₁₀, -S(O)₂R₁₀, -OS(O)₂R₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(O)OR₁₀, -C(S)R₁₀,

- C(O)NR₁₀R₁₀, -NR₁₀C(O)R₁₀, -NR₁₀C(O)NR₁₀R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, or optionally substituted phenyl, provided that R₁₀ is H, lower alkyl, or halogenated lower alkyl, and further provided that when said lower alkyl is optionally substituted, said lower alkyl can be further optionally substituted with up to 3 substituents
- 5 independently selected from F, Cl, Br, and I. This allows the lower alkyl of R₅ to be substituted with one substituent selected from -CN, -NO₂, -OR₁₀, -SR₁₀, -S(O)R₁₀, -S(O)₂R₁₀, -OS(O)₂R₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(O)OR₁₀, -C(S)R₁₀, -C(O)NR₁₀R₁₀, -NR₁₀C(O)R₁₀, -NR₁₀C(O)NR₁₀R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, or optionally substituted phenyl, and further optionally substituted with up to 3 substituents
- 10 independently selected from F, Cl, Br, and I on any carbon with sufficient valency for said substitution. This further provides that for the following optional substituents on R₅, the R₁₀ of said substituents is H, lower alkyl or halogenated lower alkyl: -OR₁₀, -SR₁₀, -S(O)R₁₀, -S(O)₂R₁₀, -OS(O)₂R₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(O)OR₁₀, -C(S)R₁₀, -C(O)NR₁₀R₁₀, -NR₁₀C(O)R₁₀, -NR₁₀C(O)NR₁₀R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀.
- 15 Optionally substituted phenyl is phenyl optionally substituted with up to 3 substituents independently selected from F, Cl, Br, I, and R₁₃ and further optionally substituted with up to 1 substituent selected from R₁₅.
- The compound of Formula I, where R₀ is H or lower alkyl, wherein R₁ is H or lower alkyl, and wherein each R₂ is absent or lower alkyl.
- 20 The compound of Formula I, where m is 2, m is 1 or m is 0.
- The compound of Formula I, where W¹ is CH. The compound of Formula I, where W¹ is N.
- The compound of Formula I, where R₀, R₁, and each R₅ are H and R₂ is absent.
- Another group of compounds of Formula I includes compounds where each R₃
- 25 is absent. Another group of compounds of Formula I includes compounds where each R₃ independently includes being absent and being any one of F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, alkenyl, halogenated alkenyl, substituted alkenyl, alkynyl, halogenated alkynyl, substituted alkynyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, substituted phenyl, -OR₁₀, -SR₁₀, -SOR₁₀, -SO₂R₁₀, -NR₁₀R₁₀, -NO₂, -C(O)R₁₀, -CN, -C(O)₂R₁₀, -C(O)NR₁₀R₁₀, -SCN, -NR₁₀C(O)R₁₀, -S(O)NR₁₀R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, R₇, or R₉.
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Another group of compounds of Formula I includes compounds where each R₃ independently includes being absent and being any one of H, F, Cl, Br, I, alkyl, halogenated alkyl, -OR₁₀, -SR₁₀, -C(O)R₁₀, -NO₂, -CN, or -C(O)NR₁₀R₁₀.

Another group of compounds of Formula I includes compounds where R₄ includes any one of the following: H, F, Cl, Br, I, alkyl, halogenated alkyl, -OR₁₀, -C(O)R₁₀, -NO₂, -CN, or -C(O)NR₁₀R₁₀.

Another group of compounds of Formula I includes compounds where W is 1H-pyrazol-1-yl, substituted at the four position with any one of the following: halogen, methyl, cyano, methylthio, aryl, R₇ or R₉. Another group of compounds of Formula I includes compounds where W is 1H-pyrazol-1-yl, substituted at the four position with phenyl optionally substituted wherever valency allows with any one of the following: halogen, lower alkyl, or -O-(lower alkyl). Another group of compounds of Formula I includes compounds where W is 1H-pyrazol-1-yl, substituted at the four position with thienyl or pyridinyl.

Another group of compounds of Formula I includes compounds where W is 1H-pyrrol-1-yl, substituted at the three position with any one of the following: halogen, methyl, cyano, methylthio, aryl, R₇ or R₉. Another group of compounds of Formula I includes compounds where W is 1H-pyrrol-1-yl, substituted at the three position with phenyl optionally substituted wherever valency allows with any one of the following: halogen, lower alkyl, or -O-(lower alkyl). Another group of compounds of Formula I includes compounds where W is 1H-pyrrol-1-yl, substituted at the three position with thienyl or pyridinyl.

Another group of compounds of Formula I includes any one or more or combination of the following as a free base or pharmaceutically acceptable salt thereof:

N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-chloro-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-bromo-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-iodo-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-methyl-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-cyano-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(methylthio)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-thien-2-yl-1H-pyrazole-1-carboxamide;

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-thien-3-yl-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-phenyl-1H-pyrazole-1-carboxamide;
 5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(2-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;
 10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;
 15 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 20 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-chloro-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-bromo-1H-pyrrole-1-carboxamide;
 25 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-iodo-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-methyl-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-cyano-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(methylthio)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-thien-2-yl-1H-pyrrole-1-carboxamide;
 30 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-thien-3-yl-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-phenyl-1H-pyrrole-1-carboxamide;

- N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
 5 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(3-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
 10 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(2-methoxyphenyl)-1H-pyrrole-1-
 carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(3-methoxyphenyl)-1H-pyrrole-1-
 carboxamide;
 N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-3-(4-methoxyphenyl)-1H-pyrrole-1-
 15 carboxamide;
 any of which is optionally substituted at either the two or six position on the
 quinuclidine with methyl, provided that if the quinuclidine is substituted at the two
 position, the quinuclidine has the 2S,3R configuration, e.g., N-[(2S,3R)-2-methyl-1-
 azabicyclo[2.2.2]oct-3-yl]-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide, or N-
 20 [(3R)-6-methyl-1-azabicyclo[2.2.2]oct-3-yl]-3-(4-methoxyphenyl)-1H-pyrrole-1-
 carboxamide.

Another group of compounds of Formula I includes any one or more or
 combination of the following as a free base or pharmaceutically acceptable salt
 25 thereof:

- Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-chloro-1H-pyrazole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-bromo-1H-pyrazole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-iodo-1H-pyrazole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-methyl-1H-pyrazole-1-carboxamide;
 30 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-cyano-1H-pyrazole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(methylthio)-1H-pyrazole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-thien-2-yl-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-thien-3-yl-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;

5 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-phenyl-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(2-fluorophenyl)-1H-pyrazole-1-carboxamide;

10 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(3-fluorophenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;

15 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;

20 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;

25 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;

30 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-chloro-1H-pyrrole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-bromo-1H-pyrrole-1-carboxamide;

Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-iodo-1H-pyrrole-1-carboxamide;

- Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-methyl-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-cyano-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(methylthio)-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-thien-2-yl-1H-pyrrole-1-carboxamide;
 5 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-thien-3-yl-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-phenyl-1H-pyrrole-1-carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(2-fluorophenyl)-1H-pyrrole-1-
 10 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(3-fluorophenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(4-fluorophenyl)-1H-pyrrole-1-
 carboxamide;
 15 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(2-chlorophenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(3-chlorophenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(4-chlorophenyl)-1H-pyrrole-1-
 20 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(2-methylphenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(3-methylphenyl)-1H-pyrrole-1-
 carboxamide;
 25 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(4-methylphenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(2-methoxyphenyl)-1H-pyrrole-1-
 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(3-methoxyphenyl)-1H-pyrrole-1-
 30 carboxamide;
 Exo-4(S)-N-(1-azabicyclo[2.2.1]hept-3-yl)-3-(4-methoxyphenyl)-1H-pyrrole-1-
 carboxamide;

- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-chloro-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-bromo-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-iodo-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-methyl-1H-pyrazole-1-carboxamide;
 5 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-cyano-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(methylthio)-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-thien-2-yl-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-thien-3-yl-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;
 10 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-phenyl-1H-pyrazole-1-carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(2-fluorophenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(3-fluorophenyl)-1H-pyrazole-1-
 15 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(4-fluorophenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(2-chlorophenyl)-1H-pyrazole-1-
 carboxamide;
 20 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(3-chlorophenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(4-chlorophenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(2-methylphenyl)-1H-pyrazole-1-
 25 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(3-methylphenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(4-methylphenyl)-1H-pyrazole-1-
 carboxamide;
 30 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(2-methoxyphenyl)-1H-pyrazole-1-
 carboxamide;
 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(3-methoxyphenyl)-1H-pyrazole-1-
 carboxamide;

- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-chloro-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-bromo-1H-pyrrole-1-carboxamide;
- 5 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-iodo-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-methyl-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-cyano-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(methylthio)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-thien-2-yl-1H-pyrrole-1-carboxamide;
- 10 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-thien-3-yl-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-phenyl-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;
- 15 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(3-chlorophenyl)-1H-pyrrole-1-
- 20 carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
- 25 N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(2-methoxyphenyl)-1H-pyrrole-1-
- 30 carboxamide;
- N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(3-methoxyphenyl)-1H-pyrrole-1-carboxamide;

N-(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide;

- N-1-azabicyclo[3.2.2]non-3-yl-4-chloro-1H-pyrazole-1-carboxamide;
- 5 N-1-azabicyclo[3.2.2]non-3-yl-4-bromo-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-iodo-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-methyl-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-cyano-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(methylthio)-1H-pyrazole-1-carboxamide;
- 10 N-1-azabicyclo[3.2.2]non-3-yl-4-thien-2-yl-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-thien-3-yl-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-phenyl-1H-pyrazole-1-carboxamide;
- 15 N-1-azabicyclo[3.2.2]non-3-yl-4-(2-fluorophenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(3-fluorophenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;
- 20 N-1-azabicyclo[3.2.2]non-3-yl-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- 25 N-1-azabicyclo[3.2.2]non-3-yl-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-chloro-1H-pyrrole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-bromo-1H-pyrrole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-iodo-1H-pyrrole-1-carboxamide;
- 30 N-1-azabicyclo[3.2.2]non-3-yl-3-methyl-1H-pyrrole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-cyano-1H-pyrrole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-(methylthio)-1H-pyrrole-1-carboxamide;
- N-1-azabicyclo[3.2.2]non-3-yl-3-thien-2-yl-1H-pyrrole-1-carboxamide;

- N-1-azabicyclo[3.2.2]non-3-yl-3-thien-3-yl-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-phenyl-1H-pyrrole-1-carboxamide;
 5 N-1-azabicyclo[3.2.2]non-3-yl-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(3-chlorophenyl)-1H-pyrrole-1-carboxamide;
 10 N-1-azabicyclo[3.2.2]non-3-yl-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(2-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 15 N-1-azabicyclo[3.2.2]non-3-yl-3-(3-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 N-1-azabicyclo[3.2.2]non-3-yl-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide;
- N-2-azabicyclo[2.2.1]hept-5-yl-4-chloro-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-bromo-1H-pyrazole-1-carboxamide;
 20 N-2-azabicyclo[2.2.1]hept-5-yl-4-iodo-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-methyl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-cyano-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(methylthio)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-thien-2-yl-1H-pyrazole-1-carboxamide;
 25 N-2-azabicyclo[2.2.1]hept-5-yl-4-thien-3-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-phenyl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(2-fluorophenyl)-1H-pyrazole-1-carboxamide;
 30 N-2-azabicyclo[2.2.1]hept-5-yl-4-(3-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;

- N-2-azabicyclo[2.2.1]hept-5-yl-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;
 5 N-2-azabicyclo[2.2.1]hept-5-yl-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-chloro-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-bromo-1H-pyrrole-1-carboxamide;
 10 N-2-azabicyclo[2.2.1]hept-5-yl-3-iodo-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-methyl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-cyano-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(methylthio)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-thien-2-yl-1H-pyrrole-1-carboxamide;
 15 N-2-azabicyclo[2.2.1]hept-5-yl-3-thien-3-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-phenyl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;
 20 N-2-azabicyclo[2.2.1]hept-5-yl-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(3-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
 25 N-2-azabicyclo[2.2.1]hept-5-yl-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(2-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-5-yl-3-(3-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 30 N-2-azabicyclo[2.2.1]hept-5-yl-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide;

 N-2-azabicyclo[2.2.1]hept-6-yl-4-chloro-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-bromo-1H-pyrazole-1-carboxamide;

- N-2-azabicyclo[2.2.1]hept-6-yl-4-iodo-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-methyl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-cyano-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(methylthio)-1H-pyrazole-1-carboxamide;
 5 N-2-azabicyclo[2.2.1]hept-6-yl-4-thien-2-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-thien-3-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-pyridin-2-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-pyridin-3-yl-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-phenyl-1H-pyrazole-1-carboxamide;
 10 N-2-azabicyclo[2.2.1]hept-6-yl-4-(2-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(3-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;
 15 N-2-azabicyclo[2.2.1]hept-6-yl-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 20 N-2-azabicyclo[2.2.1]hept-6-yl-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-chloro-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-bromo-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-iodo-1H-pyrrole-1-carboxamide;
 25 N-2-azabicyclo[2.2.1]hept-6-yl-3-methyl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-cyano-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(methylthio)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-thien-2-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-thien-3-yl-1H-pyrrole-1-carboxamide;
 30 N-2-azabicyclo[2.2.1]hept-6-yl-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-phenyl-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;

- N-2-azabicyclo[2.2.1]hept-6-yl-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(3-chlorophenyl)-1H-pyrrole-1-carboxamide;
 5 N-2-azabicyclo[2.2.1]hept-6-yl-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(2-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 10 N-2-azabicyclo[2.2.1]hept-6-yl-3-(3-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 N-2-azabicyclo[2.2.1]hept-6-yl-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-chloro-1H-pyrazole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-bromo-1H-pyrazole-1-carboxamide;
 15 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-iodo-1H-pyrazole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-methyl-1H-pyrazole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-cyano-1H-pyrazole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(methylthio)-1H-pyrazole-1-
 carboxamide;
- 20 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-thien-2-yl-1H-pyrazole-1-
 carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-thien-3-yl-1H-pyrazole-1-
 carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-pyridin-2-yl-1H-pyrazole-1-
 25 carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-pyridin-3-yl-1H-pyrazole-1-
 carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-phenyl-1H-pyrazole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(2-fluorophenyl)-1H-pyrazole-1-
 30 carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(3-fluorophenyl)-1H-pyrazole-1-
 carboxamide;

- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(4-fluorophenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide;
- 5 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(3-chlorophenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(4-chlorophenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(2-methylphenyl)-1H-pyrazole-1-carboxamide;
- 10 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(3-methylphenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(4-methylphenyl)-1H-pyrazole-1-carboxamide;
- 15 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(3-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide;
- 20 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-chloro-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-bromo-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-iodo-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-methyl-1H-pyrrole-1-carboxamide;
- 25 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-cyano-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(methylthio)-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-thien-2-yl-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-thien-3-yl-1H-pyrrole-1-carboxamide;
- 30 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-pyridin-2-yl-1H-pyrrole-1-carboxamide;
- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-pyridin-3-yl-1H-pyrrole-1-carboxamide;

- N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-phenyl-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(2-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(3-fluorophenyl)-1H-pyrrole-1-carboxamide;
 5 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(4-fluorophenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(2-chlorophenyl)-1H-pyrrole-1-carboxamide;
 10 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(3-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(4-chlorophenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(2-methylphenyl)-1H-pyrrole-1-carboxamide;
 15 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(3-methylphenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(4-methylphenyl)-1H-pyrrole-1-carboxamide;
 20 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(2-methoxyphenyl)-1H-pyrrole-1-carboxamide;
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(3-methoxyphenyl)-1H-pyrrole-1-carboxamide; or
 N-(1S, 2R, 4R)-7-azabicyclo[2.2.1]hept-2-yl-3-(4-methoxyphenyl)-1H-pyrrole-1-carboxamide.
 25

The present invention also includes a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient and optionally an anti-psychotic agent. The pharmaceutical composition is administered rectally, topically, orally, sublingually, or parenterally for a therapeutically effective interval. The pharmaceutical composition is administered to deliver a compound of Formula I in an amount of from about 0.001 to about 100 mg/kg of body weight of said mammal per day. The pharmaceutical

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composition is also administered to deliver a compound of Formula I in an amount of from about 0.1 to about 50 mg/kg of body weight of said mammal per day.

The present invention also includes a method to use a compound according to Formula I or pharmaceutically acceptable salt thereof by itself or optionally in
5 combination with an anti-psychotic agent for treating, or preparing a medicament to treat, a disease or condition, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of $\alpha 7$ nicotinic acetylcholine receptor agonist.

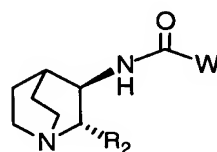
The present invention also includes a method to use a compound according to
10 Formula I or pharmaceutically acceptable salt thereof by itself or optionally in combination with an anti-psychotic agent for treating, or preparing a medicament to treat, a disease or condition, wherein the mammal would receive symptomatic relief from the administration of a therapeutically effective amount of $\alpha 7$ nicotinic acetylcholine receptor agonist, and wherein the disease, or condition is any one or
15 more or combination of the following: cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder, mood and
20 affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems in general and associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including
25 bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

The invention also concerns the synthesis of and isolation of stereospecific
30 intermediates and final compounds. Specifically, the present invention concerns the stereoselective synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine, or salts thereof. Although there are known procedures for making 1-azabicyclo[3.2.1]octan-3-amine, separation of the different stereoisomers as described herein occurs without

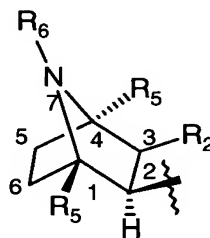
using a chiral HPLC separation procedure. The procedure within this invention results in an efficient selective synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine.

The present invention also includes the compounds of the present invention, pharmaceutical compositions containing the active compounds, and methods to treat
5 the identified diseases.

The compounds of Formula I where Azabicyclo is I have optically active centers on the quinuclidine ring. The compounds of the present invention include quinuclidines with the 2*S*, 3*R* configuration and also includes racemic mixtures and compositions of varying degrees of stereochemical purities. For example, and not by
10 limitation, compounds of Formula I include compounds with stereospecificity including:



The compounds of Formula I where Azabicyclo is VII have optically active centers on the 7-azabicyclo[2.2.1]heptane ring which can exhibit a number of
15 stereochemical configurations.



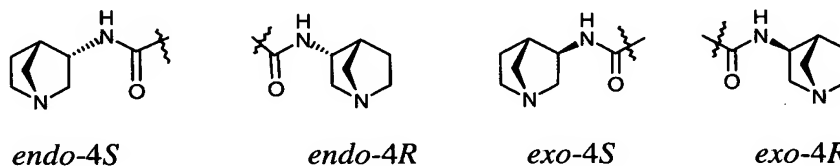
The terms *exo* and *endo* are stereochemical prefixes that describe the relative configuration of a substituent on a bridge (not a bridgehead) of a bicyclic system. If a substituent is oriented toward the larger of the other bridges, it is *endo*. If a
20 substituent is oriented toward the smaller bridge it is *exo*. Depending on the substitution on the carbon atoms, the *endo* and *exo* orientations can give rise to different stereoisomers. For instance, when carbons 1 and 4 are substituted with hydrogen and carbon 2 is bonded to a nitrogen-containing species, the *endo* orientation gives rise to the possibility of a pair of enantiomers: either the 1*S*, 2*S*, 4*R*
25 isomer or its enantiomer, the 1*R*, 2*R*, 4*S* isomer. Likewise, the *exo* orientation gives rise to the possibility of another pair of stereoisomers which are diastereomeric and C-2 epimeric with respect to the *endo* isomers: either the 1*R*, 2*S*, 4*S* isomer or its

enantiomer, the *1S*, *2R*, *4R* isomer. The compounds of this invention exist in the *exo* orientation. For example, when R_2 is absent and each R_5 is H, the absolute stereochemistry is *exo*-(*1S*, *2R*, *4R*).

Stereoselective syntheses and/or subjecting the reaction product to appropriate
 5 purification steps produces substantially optically pure materials. Suitable stereoselective synthetic procedures for producing optically pure materials are well known in the art, as are procedures for purifying racemic mixtures into optically pure fractions.

The compounds of the present invention have the *exo* orientation at the C-2
 10 carbon and *S* configuration at the C-1 carbon and the *R* configuration at the C-2 and the C-4 carbons of the 7-azabicyclo[2.2.1]heptane ring. Unexpectedly, the inventive compounds exhibit much higher activity relative to compounds lacking the *exo*, *1S*, *2R*, and *4R* stereochemistry. For example, the ratio of activities for compounds having the *exo*, *1S*, *2R*, and *4R* configuration to other stereochemical configurations
 15 may be greater than about 100. Although it is desirable that the stereochemical purity be as high as possible, absolute purity is not required. For example, pharmaceutical compositions can include one or more compounds, each having an *exo*, *1S*, *2R*, and *4R* configuration, or mixtures of compounds having *exo*, *1S*, *2R*, and *4R* and other configurations. In mixtures of compounds, those species possessing stereochemical
 20 configurations other than *exo*, *1S*, *2R*, and *4R* act as diluents and tend to lower the activity of the pharmaceutical composition. Typically, pharmaceutical compositions including mixtures of compounds possess a larger percentage of species having the *exo*, *1S*, *2R*, and *4R* configuration relative to other configurations.

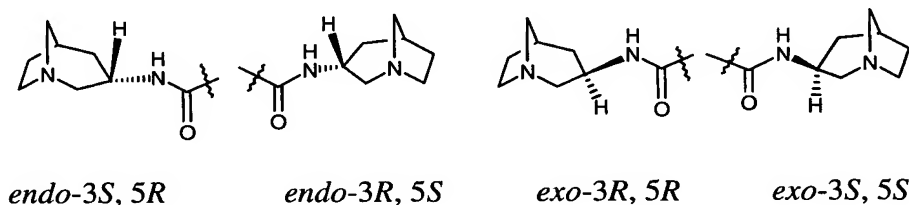
The compounds of Formula I (Azabicyclo is II) have optically active center(s)
 25 on the [2.2.1] azabicyclic ring at C3 and C4. The scope of this invention includes racemic mixtures and the separate stereoisomers of Formula I being *endo*-*4S*, *endo*-*4R*, *exo*-*4S*, *exo*-*4R*:



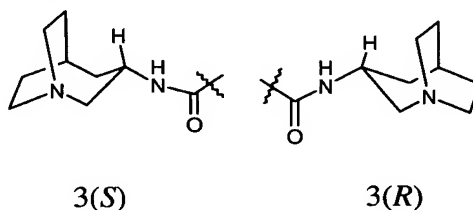
30 The *endo* isomer is the isomer where the non-hydrogen substituent at C3 of the [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges. The *exo* isomer is the isomer where the non-hydrogen substituent at C3 of the [2.2.1]

azabicyclic compound is projected toward the smaller of the two remaining bridges. Thus, there can be four separate isomers: *exo*-4(*R*), *exo*-4(*S*), *endo*-4(*R*), and *endo*-4(*S*).

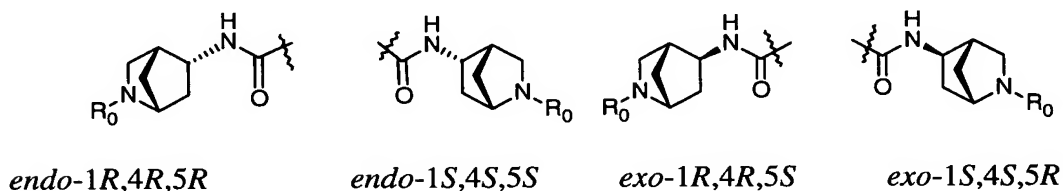
The compounds of Formula I (Azabicyclo is III) have optically active center(s) on the [3.2.1] azabicyclic ring at C3 and C5. The scope of this invention includes racemic mixtures and the separate stereoisomers of Formula I being *endo*-3*S*, 5*R*, *endo*-3*R*, 5*S*, *exo*-3*R*, 5*R*, *exo*-3*S*, 5*S*:



The compounds of Formula I (Azabicyclo is IV) have optically active centers on the [3.2.2] azabicyclic ring with one center being at C3 when R₂ is absent. The scope of this invention includes racemic mixtures and the separate stereoisomers of Formula I being 3(*S*) and 3(*R*):



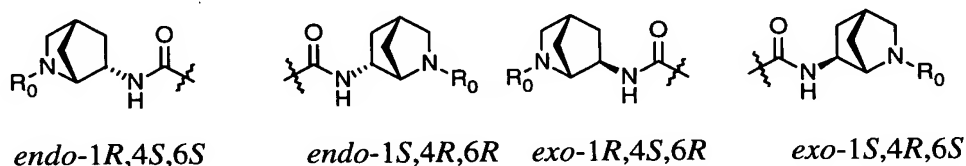
The compounds of Formula I (Azabicyclo V) have optically active center(s) on the [2.2.1] azabicyclic ring at C1, C4 and C5. The scope of this invention includes racemic mixtures and the separate stereoisomers of Formula I being (1*R*,4*R*,5*S*), (1*R*,4*R*,5*R*), (1*S*,4*S*,5*R*), (1*S*,4*S*,5*S*):



The *endo* isomer is the isomer where the non-hydrogen substituent at C5 of the [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges. The *exo* isomer is the isomer where the non-hydrogen substituent at C5 of the [2.2.1] azabicyclic compound is projected toward the smaller of the two remaining

bridges. Thus, there can be four separate isomers: *exo*-(1*R*,4*R*,5*S*), *exo*-(1*S*,4*S*,5*R*), *endo*-(1*S*,4*S*,5*S*), *endo*-(1*R*,4*R*,5*R*).

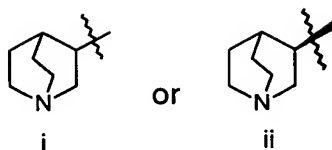
The compounds of Formula I (Azabicyclo VI) have optically active center(s) on the [2.2.1] azabicyclic ring at C1, C4 and C6. The scope of this invention includes
 5 racemic mixtures and the separate stereoisomers of Formula I being *exo*-(1*S*,4*R*,6*S*), *exo*-(1*R*,4*S*,6*R*), *endo*-(1*S*,4*R*,6*R*), and *endo*-(1*R*,4*S*,6*S*):



The *endo* isomer is the isomer where the non-hydrogen substituent at C6 of the
 10 [2.2.1] azabicyclic compound is projected toward the larger of the two remaining bridges. The *exo* isomer is the isomer where the non-hydrogen substituent at C6 of the [2.2.1] azabicyclic compound is projected toward the smaller of the two remaining bridges. Thus, there can be four separate isomers: *exo*-(1*S*,4*R*,6*S*), *exo*-(1*R*,4*S*,6*R*), *endo*-(1*S*,4*R*,6*R*), and *endo*-(1*R*,4*S*,6*S*).

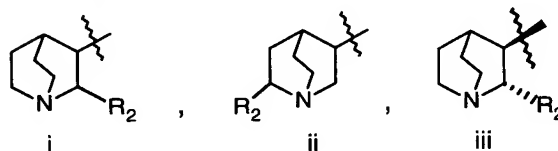
15 The compounds of the present invention having the specified stereochemistry have different levels of activity and that for a given set of values for the variable substituents one isomer may be preferred over the other isomers. Although it is desirable that the stereochemical purity be as high as possible, absolute purity is not required. This invention involves racemic mixtures and compositions of varying
 20 degrees of stereochemical purities when R₂ is absent and when R₂ is present (a substituent rather than H). This invention involves racemic mixtures and compositions of varying degrees of stereochemical purities. It is preferred to carry out stereoselective syntheses and/or to subject the reaction product to appropriate purification steps so as to produce substantially optically pure materials. Suitable
 25 stereoselective synthetic procedures for producing optically pure materials are well known in the art, as are procedures for purifying racemic mixtures into optically pure fractions.

Another embodiment of the compounds of Formula I of the present invention includes any one or more or combination of the following configurations for
 30 compounds where Azabicyclo is:



where (i) R_2 is absent (k_1 is 0) and where the compound is a racemic mixture, or (ii) R_2 is absent and where the compound is has the *R* stereochemistry at C-3 as discussed herein.

- 5 Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds where Azabicyclo is:

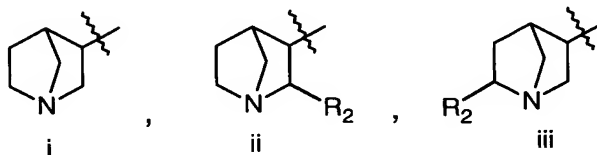


where (i) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl and where the compound is a racemic mixture;

- 10 (ii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl and where the compound is a racemic mixture; or

(iii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl and where the compound has the 3*R*, 2*S* stereochemistry as discussed herein, respectively.

- 15 Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds where Azabicyclo is:



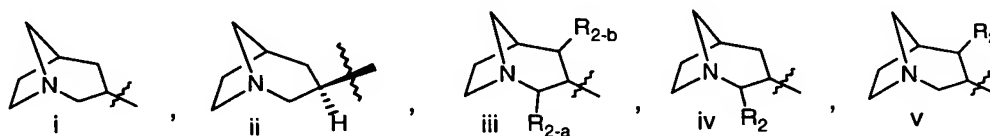
where (i) R_2 is absent (k_2 is 0);

(ii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

(iii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl,

- 20 respectively.

Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds wherein Azabicyclo is



where (i) R_2 is absent (k_3 is 0);

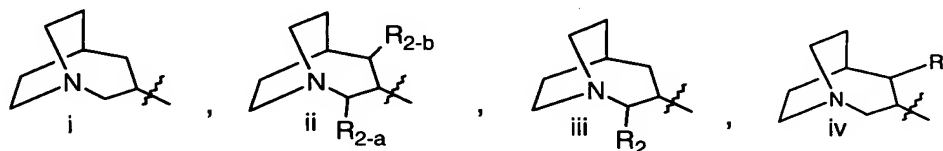
(ii) R_2 is absent and where the Azabicyclo has the stereochemistry of 3*R*, 5*R*;

(iii) k_3 is 2, R_2 is R_{2-a} and R_{2-b} , where R_{2-a} is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, and where R_{2-b} is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

5 (iv) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

(v) R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, respectively.

Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds wherein Azabicyclo is



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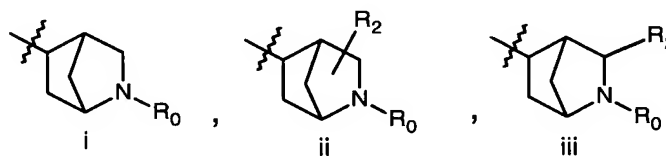
where (i) R_2 is absent (k_4 is 0);

(ii) k_4 is 2, R_2 is R_{2-a} and R_{2-b} , R_{2-a} is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl and where each R_{2-b} is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl;

15 (iii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

(iv) R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, respectively.

Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds where Azabicyclo is:



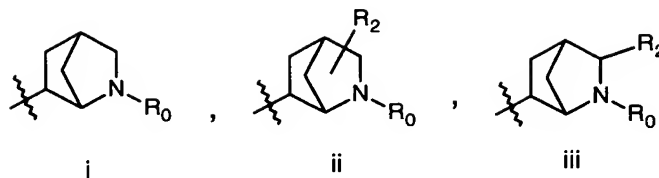
20

where (i) R_2 is absent (k_5 is 0);

(ii) R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

25 (iii) R_2 is alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, respectively.

Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds where Azabicyclo is:

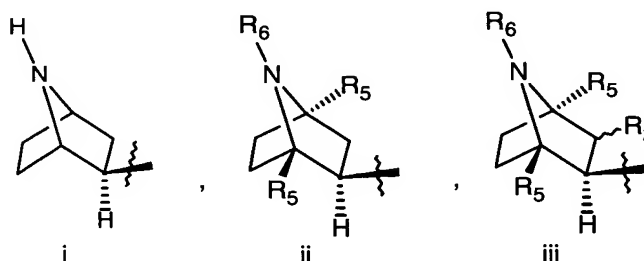


where (i) R_2 is absent (k_6 is 0);

(ii) R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; or

5 (iii) R_2 is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl, respectively.

Another group of compounds of Formula I includes any one or more or combination of the following configurations for compounds where Azabicyclo is:



10 where (i) the 7-azabicyclo[2.2.1]heptane ring moiety is the 2*R* stereoisomer;

(ii) R_2 is absent (k_7 is 0), and each R_5 may independently be H, alkyl, or substituted alkyl, and where R_6 is any one of H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents independently selected from F, Cl, Br, I, -OH, -CN, -NH₂, -NH(alkyl), or -N(alkyl)₂, and where the 7-azabicyclo[2.2.1]heptane ring

15 moiety has the 1*S*, 2*R*, 4*R* stereochemistry; or

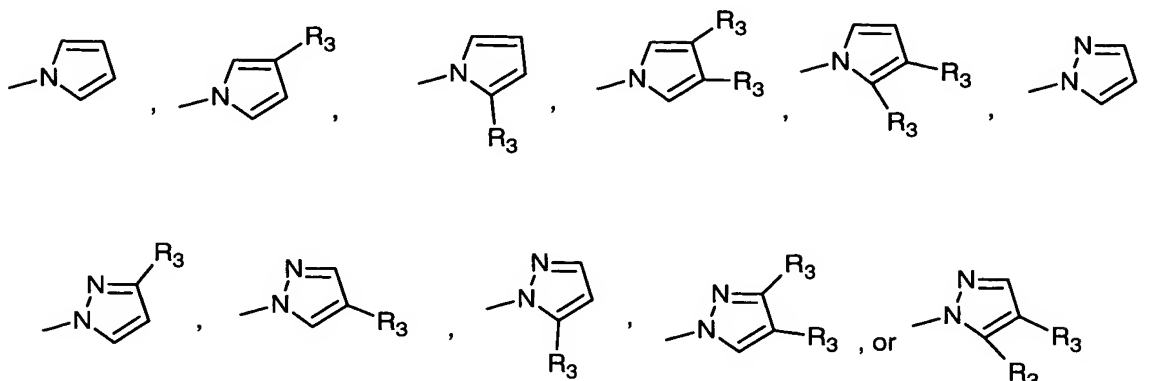
(iii) R_2 is alkyl, or substituted alkyl, and where each R_5 may independently be H, alkyl, or substituted alkyl, and where R_6 is any one of H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH₂, -NH(alkyl), or -N(alkyl)₂, and where the 7-azabicyclo[2.2.1]heptane

20 ring moiety has the 1*S*, 2*R*, 4*R* stereochemistry, respectively.

The azabicyclic moiety of Formula I is connected to W by a urea or thiourea linkage. This type of linkage imparts different physical properties to the compounds compared to the corresponding amide or thioamide. The different physical properties offer advantages in ease of formulation, reduced toxicity or a different metabolism

25 profile.

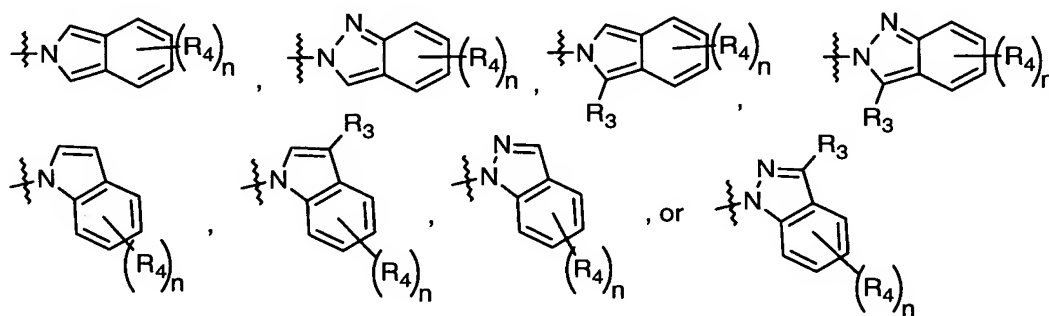
Another group of compounds of Formula I includes compounds where W is any one or more or combination of the following:



5

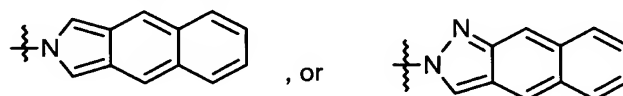
where R₃ has any definition as described herein.

Another group of compounds of Formula I includes compounds where W is any one or more or combination of the following:



10 where R₄ has any definition as described herein, and where n is 0, 1, 2, or 3.

Another group of compounds of Formula I includes compounds where W is a three-fused ring moiety and includes any one of the following:



15 The three-fused ring moiety is composed of a five-membered ring fused to a middle 6-membered ring fused to a terminal 6-membered ring. The middle 6-membered ring and the terminal 6-membered ring are each optionally substituted with one substituent selected from Br, Cl, F, I, -CN, -NO₂, -CF₃, -N(R₈)₂, -N(R₈)C(O)R₈, alkyl, alkenyl, and alkynyl.

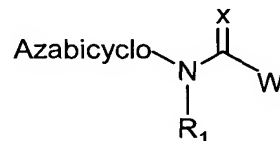
20 Further aspects and embodiments of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the examples and the appended claims. While the invention is

susceptible of embodiments in various forms, described hereafter are specific embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

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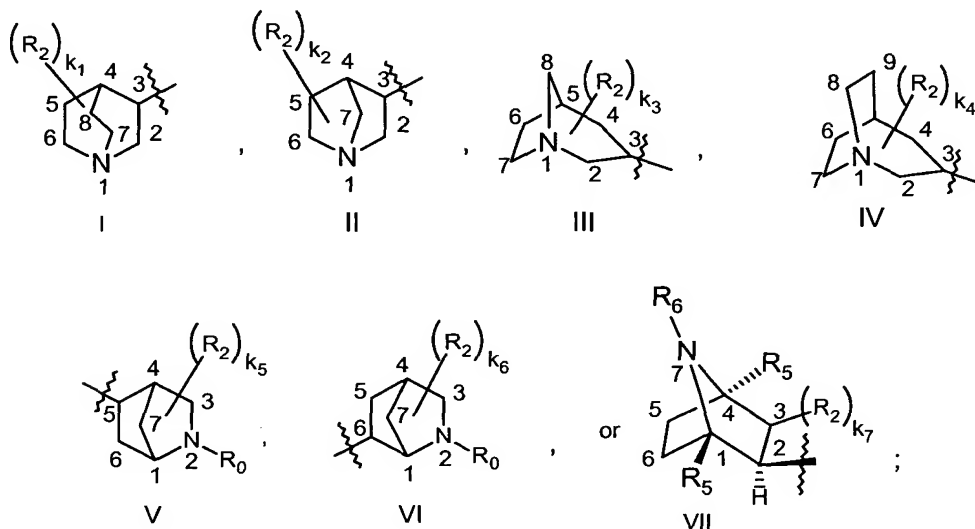
DETAILED DESCRIPTION OF THE INVENTION

Surprisingly, we have found that compounds of Formula I:

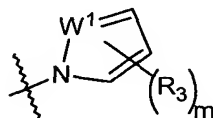


Formula I

10 wherein Azabicyclo is



W is



15

wherein W¹ is N or CH;

X is O or S;

R₀ is H, lower alkyl, substituted lower alkyl, or halogenated lower alkyl;

Lower alkyl is both straight- and branched-chain moieties having 1-4 carbon

20 atoms;

Substituted lower alkyl is lower alkyl having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(O)NR₁₀R₁₀, -NR₁₀C(O)R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 1 substituent selected from R₁₅ and further having 0-3 substituents independently selected from F, Cl, Br, or I;

Halogenated lower alkyl is lower alkyl having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

R₁ is H, alkyl, halogenated alkyl, cycloalkyl, substituted phenyl, or substituted naphthyl;

Alkyl is both straight- and branched-chain moieties having from 1-6 carbon atoms;

Halogenated alkyl is an alkyl moiety having from 1-6 carbon atoms and having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Cycloalkyl is a cyclic alkyl moiety having from 3-6 carbon atoms;

Substituted phenyl is a phenyl either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R₁₂ and 0-3 substituents independently selected from F, Cl, Br, or I;

Substituted naphthyl is a naphthalene moiety either having 1-4 substituents independently selected from F, Cl, Br, or I, or having 1 substituent selected from R₁₂ and 0-3 substituents independently selected from F, Cl, Br, or I, where the substitution can be independently on either only one ring or both rings of said naphthalene moiety;

R₂ is F, Cl, Br, I, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, or aryl; k₁, k₂, k₅, k₆, and k₇ are independently 0, or 1; k₃, and k₄ are independently 0, 1, or 2;

Substituted alkyl is an alkyl moiety from 1-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(S)R₁₀, -C(O)OR₁₀, -C(O)N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀C(O)R₁₀N(R₁₀)₂,

-NR₁₀S(O)₂R₁₀, -S(O)R₁₀, -S(O)OR₁₀, -OS(O)₂R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 0-3 substituents independently selected from F, Cl, Br, I, or R₁₃, and further having 1 substituent selected from R₁₅;

Aryl is phenyl, substituted phenyl, naphthyl, or substituted naphthyl;

5 Each R₃ is independently F, Cl, Br, I, -CN, -NO₂, alkyl, halogenated alkyl, substituted alkyl, alkenyl, halogenated alkenyl, substituted alkenyl, alkynyl, halogenated alkynyl, substituted alkynyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, aryl, R₇, R₉, -OR₁₀, -SR₁₀, -SOR₁₀,
 10 -SO₂R₁₀, -SCN, -S(O)N(R₁₀)₂, -S(O)₂N(R₁₀)₂, -C(O)R₁₀, -C(O)₂R₁₀, -C(O)N(R₁₀)₂, C(R₁₀)=N-OR₁₀, -NC(O)R₇, -NC(O)R₈, -NC(O)R₉, -N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀S(O)₂R₁₀, or two R₃ on adjacent carbon atoms may fuse to form a 6-membered ring to give a 5-6 fused, bicyclic moiety where the 6-membered ring is optionally substituted with 1-3 substituents selected from R₄;

15 m is 0, 1, or 2;

Alkenyl is straight- and branched-chain moieties having from 2-6 carbon atoms and having at least one carbon-carbon double bond;

Halogenated alkenyl is an unsaturated alkenyl moiety having from 2-6 carbon atoms and having 1 to (2n-1) substituent(s) independently selected from F, Cl, Br, or I
 20 where n is the maximum number of carbon atoms in the moiety;

Substituted alkenyl is an unsaturated alkenyl moiety having from 2-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(S)R₁₀, -C(O)OR₁₀, -C(O)N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀C(O)R₁₀N(R₁₀)₂,
 25 -NR₁₀S(O)₂R₁₀, -S(O)R₁₀, -S(O)OR₁₀, -OS(O)₂R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 0-3 substituents independently selected from F, Cl, Br, I, or R₁₃, and further having 1 substituent selected from R₁₅;

Alkynyl is straight- and branched-chained moieties having from 2-6 carbon atoms and having at least one carbon-carbon triple bond;

30 Halogenated alkynyl is an unsaturated alkynyl moiety having from 3-6 carbon atoms and having 1 to (2n-3) substituent(s) independently selected from F, Cl, Br, or I where n is the maximum number of carbon atoms in the moiety;

Substituted alkynyl is an unsaturated alkynyl moiety having from 3-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(S)R₁₀, -C(O)OR₁₀, -C(O)N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀C(O)R₁₀N(R₁₀)₂,
 5 -NR₁₀S(O)₂R₁₀, -S(O)R₁₀, -S(O)OR₁₀, -OS(O)₂R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 0-3 substituents independently selected from F, Cl, Br, I, or R₁₃, and further having 1 substituent selected from R₁₅;

Halogenated cycloalkyl is a cyclic moiety having from 3-6 carbon atoms and having 1-4 substituents independently selected from F, or Cl;

10 Substituted cycloalkyl is a cyclic moiety having from 3-6 carbon atoms and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(S)R₁₀, -C(O)OR₁₀, -C(O)N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀C(O)R₁₀N(R₁₀)₂, -NR₁₀S(O)₂R₁₀, -S(O)R₁₀, -S(O)OR₁₀, -OS(O)₂R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀,
 15 phenyl, or phenyl having 0-3 substituents independently selected from F, Cl, Br, I, or R₁₃, and further having 1 substituent selected from R₁₅;

Heterocycloalkyl is a cyclic moiety having 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R₁₉)-, or -O-;

Halogenated heterocycloalkyl is a cyclic moiety having from 4-7 atoms with
 20 1-2 atoms within the ring being -S-, -N(R₁₉)-, or -O-, and having 1-4 substituents independently selected from F, or Cl;

Substituted heterocycloalkyl is a cyclic moiety having from 4-7 atoms with 1-2 atoms within the ring being -S-, -N(R₁₉)-, or -O- and having 0-3 substituents independently selected from F, Cl, Br, or I and further having 1 substituent selected
 25 from R₇, R₉, -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(S)R₁₀, -C(O)OR₁₀, -C(O)N(R₁₀)₂, -NR₁₀C(O)R₁₀, -NR₁₀C(O)R₁₀N(R₁₀)₂, -NR₁₀S(O)₂R₁₀, -S(O)R₁₀, -S(O)OR₁₀, -OS(O)₂R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 0-3 substituents independently selected from F, Cl, Br, I, or R₁₃, and further having 1 substituent selected from R₁₅;

30 Lactam heterocycloalkyl is a cyclic moiety having from 4-7 atoms with one atom being only nitrogen with the bond to the lactam heterocycloalkyl thru said atom being only nitrogen and having a =O on a carbon adjacent to said nitrogen, and having

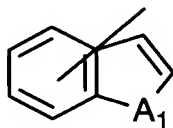
up to 1 additional ring atom being oxygen, sulfur, or nitrogen and further having 0-2 substituents selected from F, Cl, Br, I, or R_{15} where valency allows;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogenated cycloalkyl, halogenated heterocycloalkyl, -OR₈, -SR₈, -S(O)₂R₈, -S(O)R₈, -OS(O)₂R₈, -N(R₈)₂, -C(O)R₈,
 5 -C(S)R₈, -C(O)OR₈, -CN, -C(O)N(R₈)₂, -NR₈C(O)R₈, -S(O)₂N(R₈)₂, -NR₈S(O)₂R₈, -NO₂, -N(R₈)C(O)N(R₈)₂, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, lactam heterocycloalkyl, phenyl, phenyl having 0-4 substituents independently selected from F, Cl, Br, I and R_{15} ,
 10 naphthyl, naphthyl having 0-4 substituents independently selected from F, Cl, Br, I, or R_{15} , or two R_4 on adjacent carbon atoms may combine to form a three-ring-fused-5-6-6 system optionally substituted with up to 3 substituents independently selected from Br, Cl, F, I, -CN, -NO₂, -CF₃, -N(R₈)₂, -N(R₈)C(O)R₈, alkyl, alkenyl, and alkynyl;

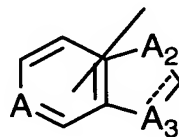
Each R_5 is independently H, alkyl, or substituted alkyl;

15 R_6 is H, alkyl, an amino protecting group, or an alkyl group having 1-3 substituents selected from F, Cl, Br, I, -OH, -CN, -NH₂, -NH(alkyl), or -N(alkyl)₂;

R_7 is 5-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms independently selected from the group consisting of -O-, =N-, -N(R₁₄)-, and -S-, and having 0-1 substituent selected from R_{15} , and further having 0-3
 20 substituents independently selected from F, Cl, Br, or I, or R_7 is 9-membered fused-ring moieties having a 6-membered ring fused to a 5-membered ring and having the formula

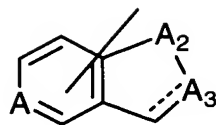


wherein A_1 is O, S, or NR₁₄,



25

wherein A is CR₁₇ or N, and each A_2 or A_3 is independently selected from CR₁₇, O, S, N, or NR₁₄, or



wherein A is CR₁₇ or N, and each A₂ or A₃ is independently selected from CR₁₇, O, S, N, or NR₁₄, and, each 9-membered fused-ring moiety having 0-1 substituent selected from R₁₅, and further having 0-3 substituent(s) independently selected from F, Cl, Br, or I, and having a bond directly or indirectly attached to the core molecule where valency allows in either the 6-membered or the 5-membered ring of the fused-ring moiety;

Each R₈ is independently H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, substituted heterocycloalkyl, phenyl, or phenyl substituted with 0-4 independently selected from F, Cl, Br, I, or R₁₅;

R₉ is 6-membered heteroaromatic mono-cyclic moieties containing within the ring 1-3 heteroatoms selected from =N- and having 0-1 substituent selected from R₁₅ and 0-3 substituent(s) independently selected from F, Cl, Br, or I, or R₉ is

10-membered heteroaromatic bi-cyclic moieties containing within one or both rings 1-3 heteroatoms selected from =N-, including, but not limited to, quinolinyl or isoquinolinyl, each 10-membered fused-ring moiety having 0-1 substituent selected from R₁₅, and 0-3 substituent(s) independently selected from F, Cl, Br, or I and having a bond directly or indirectly attached to the core molecule where valency allows;

Each R₁₀ is independently H, alkyl, cycloalkyl, heterocycloalkyl, alkyl substituted with 1 substituent selected from R₁₃, cycloalkyl substituted with 1 substituent selected from R₁₃, heterocycloalkyl substituted with 1 substituent selected from R₁₃, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, phenyl, or substituted phenyl;

Each R₁₁ is independently H, alkyl, cycloalkyl, heterocyclo-alkyl, halogenated alkyl, halogenated cycloalkyl, or halogenated heterocycloalkyl;

R₁₂ is -NO₂, -CN, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, substituted alkyl, substituted cycloalkyl, substituted heterocycloalkyl, -OR₁₁, -SR₁₁, -N(R₁₁)₂, -C(O)R₁₁, -C(O)N(R₁₁)₂, -NR₁₁C(O)R₁₁, -S(O)₂N(R₁₁)₂, or -NR₁₁S(O)₂R₁₁;

R₁₃ is -OR₁₁, -SR₁₁, -N(R₁₁)₂, -C(O)R₁₁, -SOR₁₁, -SO₂R₁₁, -C(O)N(R₁₁)₂, -CN, -CF₃, -NR₁₁C(O)R₁₁, -S(O)₂N(R₁₁)₂, -NR₁₁S(O)₂R₁₁, or -NO₂;

R₁₄ is independently H, alkyl, halogenated alkyl, limited substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, heterocycloalkyl, halogenated heterocycloalkyl, or substituted heterocycloalkyl;

R₁₅ is alkyl, substituted alkyl, halogenated alkyl, -OR₁₁, -CN, -NO₂, -N(R₁₀)₂;

5 R₁₇ is H, alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, R₁₈, -OR₁₁, -SR₁₁, -N(R₁₁)₂, -NR₁₁S(O)₂R₁₁, F, Cl, Br, or I, or a bond directly or indirectly attached to the core molecule, provided that there is only one said bond to the core molecule within the 9-membered fused-ring moiety, further provided that the fused-ring moiety has 0-1 substituent selected
10 from alkyl, cycloalkyl, heterocycloalkyl, halogenated alkyl, halogenated cycloalkyl, halogenated heterocycloalkyl, R₁₈, -OR₁₁, -SR₁₁, -NR₁₁R₁₁, -C(O)R₁₁, -NO₂, -C(O)NR₁₁R₁₁, -CN, -NR₁₁C(O)R₁₁, -S(O)₂NR₁₁R₁₁, or -NR₁₁S(O)₂R₁₁, and further provided that the fused-ring moiety has 0-3 substituent(s) selected from F, Cl, Br, or I;

R₁₈ is alkyl, cycloalkyl, heterocycloalkyl, any of which is substituted with 0-3
15 substituents independently selected from F, Cl, Br, or I and further substituted with 1 substituent selected from -NO₂, -CN, -OR₁₀, -SR₁₀, -NR₁₀R₁₀, -C(O)R₁₀, -C(O)NR₁₀R₁₀, -NR₁₀C(O)R₁₀, -S(O)₂NR₁₀R₁₀, -NR₁₀S(O)₂R₁₀, phenyl, or phenyl having 1 substituent selected from R₁₅ and further having 0-3 substituents independently selected from F, Cl, Br, or I;

20 R₁₉ is H, alkyl, halogenated alkyl, substituted alkyl, cycloalkyl, halogenated cycloalkyl, substituted cycloalkyl, phenyl, or phenyl having 0-4 substituents independently selected from F, Cl, Br, I, and R₁₅;

or pharmaceutical composition, pharmaceutically acceptable salt, racemic mixture, or pure enantiomer thereof useful to treat any one of or combination of
25 cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as Alzheimer's disease, pre-senile dementia (mild cognitive impairment), senile dementia, schizophrenia, psychosis, attention deficit disorder, attention deficit hyperactivity disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury,
30 behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, depression, general anxiety disorder, age-related macular degeneration, Parkinson's disease, tardive dyskinesia, Pick's disease, post

traumatic stress disorder, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependant drug cessation, Gilles de la Tourette's Syndrome, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

5

In another aspect, the invention includes methods of treating a mammal suffering from schizophrenia or psychosis by administering compounds of Formula I in conjunction with antipsychotic drugs. The compounds of Formula I and the antipsychotic drugs can be administered simultaneously or at separate intervals.

10 When administered simultaneously the compounds of Formula I and the antipsychotic drugs can be incorporated into a single pharmaceutical composition. Alternatively, two separate compositions, i.e., one containing compounds of Formula I and the other containing antipsychotic drugs, can be administered simultaneously.

The present invention also includes the intermediates, the processes to make
15 them and the active compounds of Formula I, pharmaceutical compositions including the active compounds, and methods to treat the identified diseases.

Abbreviations which are well known to one of ordinary skill in the art may be used (e.g., "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" or "hr" for hour or hours, min for minute or minutes, and "rt" or "RT" for room temperature).

20 All temperatures are in degrees Centigrade.

Room temperature is within the range of 15-25 degrees Celsius.

AChR refers to acetylcholine receptor.

nAChR refers to nicotinic acetylcholine receptor.

Pre-senile dementia is also known as mild cognitive impairment.

25 5HT₃R refers to the serotonin-type 3 receptor.

α -btx refers to α -bungarotoxin.

FLIPR refers to a device marketed by Molecular Devices, Inc. designed to precisely measure cellular fluorescence in a high throughput whole-cell assay. (Schroeder et. al., *J. Biomolecular Screening*, 1(2), p 75-80, 1996).

30 TLC refers to thin-layer chromatography.

HPLC refers to high pressure liquid chromatography.

MeOH refers to methanol.

EtOH refers to ethanol.

IPA refers to isopropyl alcohol.

THF refers to tetrahydrofuran.

DMSO refers to dimethylsulfoxide.

DMF refers to *N,N*-dimethylformamide.

5 EtOAc refers to ethyl acetate.

TMS refers to tetramethylsilane.

TEA refers to triethylamine.

DIEA refers to *N,N*-diisopropylethylamine.

MLA refers to methyllycaconitine.

10 Ether refers to diethyl ether.

HATU refers to O-(7-azabenzotriazol-1-yl)-*N,N,N'*, *N'*-tetramethyluronium hexafluorophosphate.

DBU refers to 1,8-diazobicyclo[5.4.0]undec-7-one.

CDI refers to carbonyl diimidazole.

15 NMO refers to *N*-methylmorpholine-*N*-oxide.

TPAP refers to tetrapropylammonium perruthenate.

Halogen is F, Cl, Br, or I.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer “i” to the integer “j” carbon atoms, inclusive. Thus, for example, C₁₋₆ alkyl refers to alkyl of one to six carbon atoms.

One will recognize that where alkyl, halogenated alkyl, or substituted alkyl is allowed, lower alkyl, halogenated lower alkyl and substituted lower alkyl would also be allowed, respectively.

Non-inclusive examples of heteroaryl compounds that fall within the definitions of R₇ and R₉ include, but are not limited to, thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, 30 indolyl, benzoxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, pyrrolyl, isoquinolinyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, quinazolinyl, quinoxaliny, naphthridinyl, furopyridinyl,

pyrrolopyridinyl, or thienopyridinyl. All isomeric forms of the non-inclusive named moieties are included, e.g., benzofuranyl includes 1-benzofuran-2-yl, 1-benzofuran-3-yl, 1-benzofuran-4-yl, 1-benzofuran-5-yl, 1-benzofuran-6-yl, 1-benzofuran-7-yl, 2-benzofuran-1-yl, 2-benzofuran-2-yl, 2-benzofuran-3-yl, 2-benzofuran-4-yl, or 2-benzofuran-5-yl. The non-inclusive examples of R₇ and R₉ may be substituted as allowed within the respective definition of R₇ and R₉ as valency allows. One of ordinary skill in the art can identify the allowed substitution by comparing the non-inclusive examples with the respective definitions of R₇ and R₉.

Non-inclusive examples of heterocycloalkyl include, but are not limited to, tetrahydrofurano, tetrahydropyrano, morpholino, pyrrolidino, piperidino, piperazine, azetidino, azetidinono, oxindolo, dihydroimidazolo, pyrrolidino, or isoxazolinyl.

Mammal denotes human and other mammals.

Brine refers to an aqueous saturated sodium chloride solution.

Equ means molar equivalents.

IR refers to infrared spectroscopy.

Lv refers to leaving groups within a molecule, including Cl, OH, or mixed anhydride.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

MS refers to mass spectrometry expressed as m/e or mass/charge unit. HRMS refers to high resolution mass spectrometry expressed as m/e or mass/charge unit. [M+H]⁺ refers to an ion composed of the parent plus a proton. [M-H]⁻ refers to an ion composed of the parent minus a proton. [M+Na]⁺ refers to an ion composed of the parent plus a sodium ion. [M+K]⁺ refers to an ion composed of the parent plus a potassium ion. EI refers to electron impact. ESI refers to electrospray ionization. CI refers to chemical ionization. FAB refers to fast atom bombardment.

Amino protecting group includes, but is not limited to, carbobenzyloxy (CBz), *tert* butoxy carbonyl (BOC) and the like. Examples of other suitable amino protecting groups are known to person skilled in the art and can be found in "Protective Groups in Organic synthesis," 3rd Edition, authored by Theodora Greene and Peter Wuts.

Compounds of the present invention may be in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and

organic bases, and salts prepared from inorganic acids, and organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, ferric, ferrous, lithium, magnesium, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N, N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and the like. Salts derived from inorganic acids include salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, phosphorous acid and the like. Salts derived from pharmaceutically acceptable organic non-toxic acids include salts of C₁₋₆ alkyl carboxylic acids, di-carboxylic acids, and tri-carboxylic acids such as acetic acid, propionic acid, fumaric acid, succinic acid, tartaric acid, maleic acid, adipic acid, and citric acid, and aryl and alkyl sulfonic acids such as toluene sulfonic acids and the like.

By the term "effective amount" of a compound as provided herein is meant a nontoxic but sufficient amount of the compound(s) to provide the desired effect. As pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease that is being treated, the particular compound(s) used, the mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation.

The amount of therapeutically effective compound(s) that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound(s) employed, and thus may vary widely. The compositions contain well known carriers and excipients in addition to a therapeutically effective amount of compounds of Formula I. The

pharmaceutical compositions may contain active ingredient in the range of about 0.001 to 100 mg/kg/day for an adult, preferably in the range of about 0.1 to 50 mg/kg/day for an adult. A total daily dose of about 1 to 1000 mg of active ingredient may be appropriate for an adult. The daily dose can be administered in one to four
5 doses per day.

In addition to the compound(s) of Formula I, the composition for therapeutic use may also comprise one or more non-toxic, pharmaceutically acceptable carrier materials or excipients. The term "carrier" material or "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier and/or diluent and/or
10 adjuvant, or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives,
15 wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Acceptable excipients include lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of
20 phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose, or other methods known to those skilled in the art. For oral
25 administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. If desired, other active ingredients may be included in the composition.

In addition to the oral dosing, noted above, the compositions of the present invention may be administered by any suitable route, in the form of a pharmaceutical
30 composition adapted to such a route, and in a dose effective for the treatment intended. The compositions may, for example, be administered parenterally, e.g., intravascularly, intraperitoneally, subcutaneously, or intramuscularly. For parenteral administration, saline solution, dextrose solution, or water may be used as a suitable

carrier. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

- 5 The compounds may be dissolved in water, polyethylene glycol, propylene glycol, EtOH, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

- The serotonin type 3 receptor (5HT₃R) is a member of a superfamily of ligand-gated ion channels, which includes the muscle and neuronal nAChR, the glycine receptor, and the γ -aminobutyric acid type A receptor. Like the other members of this receptor superfamily, the 5HT₃R exhibits a large degree of sequence homology with α 7 nAChR but functionally the two ligand-gated ion channels are very different. For example, α 7 nAChR is rapidly inactivated, is highly permeable to calcium and is
15 activated by acetylcholine and nicotine. On the other hand, 5HT₃R is inactivated slowly, is relatively impermeable to calcium and is activated by serotonin. These experiments suggest that the α 7 nAChR and 5HT₃R proteins have some degree of homology, but function very differently. Indeed the pharmacology of the channels is very different. For example, Ondansetron, a highly selective 5HT₃R antagonist, has
20 little activity at the α 7 nAChR. The converse is also true. For example, GTS-21, a highly selective α 7 nAChR agonist, has little activity at the 5HT₃R.

- α 7 nAChR is a ligand-gated Ca⁺⁺ channel formed by a homopentamer of α 7 subunits. Previous studies have established that α -bungarotoxin (α -btx) binds selectively to this homopentameric, α 7 nAChR subtype, and that α 7 nAChR has a high
25 affinity binding site for both α -btx and methyllycaconitine (MLA). α 7 nAChR is expressed at high levels in the hippocampus, ventral tegmental area and ascending cholinergic projections from nucleus basalis to thalamocortical areas. α 7 nAChR agonists increase neurotransmitter release, and increase cognition, arousal, attention, learning and memory.

- 30 Data from human and animal pharmacological studies establish that nicotinic cholinergic neuronal pathways control many important aspects of cognitive function including attention, learning and memory (Levin, E.D., *Psychopharmacology*, 108:417-31, 1992; Levin, E.D. and Simon B.B., *Psychopharmacology*, 138:217-30,

1998). For example, it is well known that nicotine increases cognition and attention in humans. ABT-418, a compound that activates $\alpha 4\beta 2$ and $\alpha 7$ nAChR, improves cognition and attention in clinical trials of Alzheimer's disease and attention-deficit disorders (Potter, A. et. al., *Psychopharmacology (Berl.)*, 142(4):334-42, Mar. 1999; 5 Wilens, T. E. et. al., *Am. J. Psychiatry*, 156(12):1931-7, Dec. 1999). It is also clear that nicotine and selective but weak $\alpha 7$ nAChR agonists increase cognition and attention in rodents and non-human primates.

Schizophrenia is a complex multifactorial illness caused by genetic and non-genetic risk factors that produce a constellation of positive and negative symptoms. 10 The positive symptoms include delusions and hallucinations and the negative symptoms include deficits in affect, attention, cognition and information processing. No single biological element has emerged as a dominant pathogenic factor in this disease. Indeed, it is likely that schizophrenia is a syndrome that is produced by the combination of many low penetrance risk factors. Pharmacological studies 15 established that dopamine receptor antagonists are efficacious in treating the overt psychotic features (positive symptoms) of schizophrenia such as hallucinations and delusions. Clozapine, an "atypical" antipsychotic drug, is novel because it is effective in treating both the positive and some of the negative symptoms of this disease. Clozapine's utility as a drug is greatly limited because continued use leads to an 20 increased risk of agranulocytosis and seizure. No other antipsychotic drug is effective in treating the negative symptoms of schizophrenia. This is significant because the restoration of cognitive functioning is the best predictor of a successful clinical and functional outcome of schizophrenic patients (Green, M.F., *Am J Psychiatry*, 153:321-30, 1996). By extension, it is clear that better drugs are needed to treat the cognitive 25 disorders of schizophrenia in order to restore a better state of mental health to patients with this disorder.

One aspect of the cognitive deficit of schizophrenia can be measured by using the auditory event-related potential (P50) test of sensory gating. In this test, electroencephalographic (EEG) recordings of neuronal activity of the hippocampus 30 are used to measure the subject's response to a series of auditory "clicks" (Adler, L.E. et. al., *Biol. Psychiatry*, 46:8-18, 1999). Normal individuals respond to the first click with greater degree than to the second click. In general, schizophrenics and schizotypal patients respond to both clicks nearly the same (Cullum, C.M. et. al.,

Schizophr. Res., 10:131-41, 1993). These data reflect a schizophrenic's inability to "filter" or ignore unimportant information. The sensory gating deficit appears to be one of the key pathological features of this disease (Cadenhead, K.S. et. al., *Am. J. Psychiatry*, 157:55-9, 2000). Multiple studies show that nicotine normalizes the sensory deficit of schizophrenia (Adler, L.E. et. al., *Am. J. Psychiatry*, 150:1856-61, 1993). Pharmacological studies indicate that nicotine's effect on sensory gating is via the $\alpha 7$ nAChR (Adler, L.E. et. al., *Schizophr. Bull.*, 24:189-202, 1998). Indeed, the biochemical data indicate that schizophrenics have 50% fewer of $\alpha 7$ nAChR receptors in the hippocampus, thus giving a rationale to partial loss of $\alpha 7$ nAChR functionality (Freedman, R. et. al., *Biol. Psychiatry*, 38:22-33, 1995). Interestingly, genetic data indicate that a polymorphism in the promoter region of the $\alpha 7$ nAChR gene is strongly associated with the sensory gating deficit in schizophrenia (Freedman, R. et. al., *Proc. Nat'l Acad. Sci. USA*, 94(2):587-92, 1997; Myles-Worsley, M. et. al., *Am. J. Med. Genet*, 88(5):544-50, 1999). To date, no mutation in the coding region of the $\alpha 7$ nAChR has been identified. Thus, schizophrenics express the same $\alpha 7$ nAChR as non-schizophrenics.

Selective $\alpha 7$ nAChR agonists may be found using a functional assay on FLIPR (see WO 00/73431 A2). FLIPR is designed to read the fluorescent signal from each well of a 96 or 384 well plate as fast as twice a second for up to 30 minutes. This assay may be used to accurately measure the functional pharmacology of $\alpha 7$ nAChR and 5HT₃R. To conduct such an assay, one uses cell lines that expressed functional forms of the $\alpha 7$ nAChR using the $\alpha 7/5$ -HT₃ channel as the drug target and cell lines that expressed functional 5HT₃R. In both cases, the ligand-gated ion channel was expressed in SH-EP1 cells. Both ion channels can produce robust signal in the FLIPR assay.

The compounds of the present invention are $\alpha 7$ nAChR agonists and may be used to treat a wide variety of diseases. For example, they may be used in treating schizophrenia, or psychosis.

Schizophrenia is a disease having multiple aspects. Currently available drugs are generally aimed at controlling the positive aspects of schizophrenia, such as delusions. One drug, Clozapine, is aimed at a broader spectrum of symptoms associated with schizophrenia. This drug has many side effects and is thus not suitable for many patients. Thus, there is a need for a drug to treat the cognitive and

attention deficits associated with schizophrenia. Similarly, there is a need for a drug to treat the cognitive and attention deficits associated with schizoaffective disorders, or similar symptoms found in the relatives of schizophrenic patients.

Psychosis is a mental disorder characterized by gross impairment in the patient's perception of reality. The patient may suffer from delusions, and hallucinations, and may be incoherent in speech. His behavior may be agitated and is often incomprehensible to those around him. In the past, the term psychosis has been applied to many conditions that do not meet the stricter definition given above. For example, mood disorders were named as psychoses.

There are a variety of antipsychotic drugs. The conventional antipsychotic drugs include Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Perphenazine, Pimozide, Thioridazine, Thiothixene, and Trifluoperazine. These drugs all have an affinity for the dopamine 2 receptor.

These conventional antipsychotic drugs have several side effects, including sedation, weight gain, tremors, elevated prolactin levels, akathisia (motor restlessness), dystonia and muscle stiffness. These drugs may also cause tardive dyskinesia. Unfortunately, only about 70% of patients with schizophrenia respond to conventional antipsychotic drugs. For these patients, atypical antipsychotic drugs are available.

Atypical antipsychotic drugs generally are able to alleviate positive symptoms of psychosis while also improving negative symptoms of the psychosis to a greater degree than conventional antipsychotics. These drugs may improve neurocognitive deficits. Extrapyramidal (motor) side effects are not as likely to occur with the atypical antipsychotic drugs, and thus, these atypical antipsychotic drugs have a lower risk of producing tardive dyskinesia. Finally these atypical antipsychotic drugs cause little or no elevation of prolactin. Unfortunately, these drugs are not free of side effects. Although these drugs each produce different side effects, as a group the side effects include: agranulocytosis; increased risk of seizures, weight gain, somnolence, dizziness, tachycardia, decreased ejaculatory volume, and mild prolongation of QTc interval.

In a combination therapy to treat multiple symptoms of diseases including schizophrenia, the compounds of Formula I and the anti-psychotic drugs can be administered simultaneously or at separate intervals. When administered

simultaneously the compounds of Formula I and the anti-psychotic drugs can be incorporated into a single pharmaceutical composition, e.g., a pharmaceutical combination therapy composition. Alternatively, two separate compositions, i.e., one containing compounds of Formula I and the other containing anti-psychotic drugs, can be administered simultaneously. Examples of anti-psychotic drugs, in addition to those listed above, include, but are not limited to, Thorazine, Mellaril, Trilafon, Navane, Stelazine, Permitil, Prolixin, Risperdal, Zyprexa, Seroquel, ZELDOX, Acetophenazine, Carphenazine, Chlorprothixene, Droperidol, Loxapine, Mesoridazine, Molindone, Ondansetron, Pimozide, Prochlorperazine, and Promazine.

10 A pharmaceutical combination therapy composition can include therapeutically effective amounts of the compounds of Formula I, noted above, and a therapeutically effective amount of anti-psychotic drugs. These compositions may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered rectally, topically, orally, sublingually, or parenterally and maybe formulated as sustained relief dosage forms and the like.

20 When separately administered, therapeutically effective amounts of compositions containing compounds of Formula I and anti-psychotic drugs are administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. A therapeutically effective interval is a period of time beginning when one of either (a) the compounds of Formula I, or (b) the anti-psychotic drugs is administered to a human and ending at the limit of the beneficial effect in the treatment of schizophrenia or psychosis of the combination of (a) and (b). The methods of administration of the compounds of Formula I and the anti-psychotic drugs may vary. Thus, either agent or both agents may be administered rectally, topically, orally, sublingually, or parenterally.

30 As discussed, the compounds of the present invention are $\alpha 7$ nAChR agonists. Therefore, as another aspect of the present invention, the compounds of the present invention may be used to treat a variety of diseases including cognitive and attention deficit symptoms of Alzheimer's, neurodegeneration associated with diseases such as

Alzheimer's disease, pre-senile dementia (also known as mild cognitive impairment), and senile dementia.

Alzheimer's disease has many aspects, including cognitive and attention deficits. Currently, these deficits are treated with cholinesterase inhibitors. These inhibitors slow the break down of acetylcholine, and thereby provide a general nonspecific increase in the activity of the cholinergic nervous system. Since the drugs are nonspecific, they have a wide variety of side effects. Thus, there is a need for a drug that stimulates a portion of the cholinergic pathways and thereby provides improvement in the cognitive and attention deficits associated with Alzheimer's disease without the side effects created by nonspecific stimulation of the cholinergic pathways.

Neurodegeneration is a common problem associated with diseases such as Alzheimer's disease. While the current drugs treat some of the symptoms of this disease, they do not control the underlying pathology of the disease. Accordingly, it would be desirable to provide a drug that can slow the progress of Alzheimer's disease.

Pre-senile dementia (mild cognitive impairment) concerns memory impairment rather than attention deficit problems and otherwise unimpaired cognitive functioning. Mild cognitive impairment is distinguished from senile dementia in that mild cognitive impairment involves a more persistent and troublesome problem of memory loss for the age of the patient. There currently is no medication specifically identified for treatment of mild cognitive impairment, due somewhat to the newness of identifying the disease. Therefore, there is a need for a drug to treat the memory problems associated with mild cognitive impairment.

Senile dementia is not a single disease state. However, the conditions classified under this name frequently include cognitive and attention deficits. Generally, these deficits are not treated. Accordingly, there is a need for a drug that provides improvement in the cognitive and attention deficits associated with senile dementia.

30

As discussed, the compounds of the present invention are $\alpha 7$ nAChR agonists. Therefore, yet other diseases to be treated with compounds of the present invention include treating the cognitive and attention deficits as well as the neurodegeneration

associated with any one or more or combination of the following: attention deficit disorder, attention deficit hyperactivity disorder, depression, anxiety, general anxiety disorder, post traumatic stress disorder, mood and affective disorders, amyotrophic lateral sclerosis, borderline personality disorder, traumatic brain injury, behavioral and cognitive problems associated with brain tumors, AIDS dementia complex, dementia associated with Down's syndrome, dementia associated with Lewy Bodies, Huntington's disease, Parkinson's disease, tardive dyskinesia, Pick's disease, dysregulation of food intake including bulimia and anorexia nervosa, withdrawal symptoms associated with smoking cessation and dependent drug cessation, Gilles de la Tourette's Syndrome, age-related macular degeneration, glaucoma, neurodegeneration associated with glaucoma, or symptoms associated with pain.

Attention deficit disorder is generally treated with methylphenidate, an amphetamine-like molecule that has some potential for abuse. Accordingly, it would be desirable to provide a drug that treats attention deficit disorder while having fewer side effects than the currently used drug.

Attention deficit hyperactivity disorder, otherwise known as ADHD, is a neurobehavioral disorder affecting 3-5% of all American children. ADHD concerns cognitive alone or both cognitive and behavioral actions by interfering with a person's ability to stay on a task and to exercise age-appropriate inhibition. Several types of ADHD exist: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype. Treatment may include medications such as methylphenidate, dextroamphetamine, or pemoline, which act to decrease impulsivity and hyperactivity and to increase attention. No "cure" for ADHD currently exists. Children with the disorder seldom outgrow it; therefore, there is a need for appropriate medicaments.

Depression is a mood disorder of varying lengths of normally several months to more than two years and of varying degrees of feelings involving sadness, despair, and discouragement. The heterocyclic antidepressants (HCA's) are currently the largest class of antidepressants, but monoamine oxidase inhibitors (MAOI's) are used in particular types of depression. Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects from HCA's can also include seizures and behavioral symptoms. The main side effects

from using MAOI's occur from dietary and drug interactions. Therefore, agents with fewer side effects would be useful.

Anxiety disorders (disorders with prominent anxiety or phobic avoidance), represent an area of unmet medical needs in the treatment of psychiatric illness. See
5 Diagnostic & Statistical Manual of Mental Disorders, IV (1994), pp 393-394, for various disease forms of anxiety.

General anxiety disorder (GAD) occurs when a person worries about things such as family, health, or work when there is no reason to worry and is unable not to worry. About 3 to 4% of the U.S. population has GAD during the course of a year.
10 GAD most often strikes people in childhood or adolescence, but can begin in adulthood, too. It affects women more often than men. Currently, treatment involves cognitive-behavioral therapy, relaxation techniques, and biofeedback to control muscle tension and medications such as benzodiazepines, imipramine, and buspirone. These drugs are effective but all have side-effect liabilities. Therefore, there is a need
15 of a pharmaceutical agent to address the symptoms with fewer side effects.

Anxiety also includes post-traumatic stress disorder (PTSD), which is a form of anxiety triggered by memories of a traumatic event that directly affected the patient or that the patient may have witnessed. The disorder commonly affects survivors of traumatic events including sexual assault, physical assault, war, torture, natural
20 disasters, an automobile accident, an airplane crash, a hostage situation, or a death camp. The affliction also can affect rescue workers at an airplane crash or a mass shooting, someone who witnessed a tragic accident or someone who has unexpectedly lost a loved one. Treatment for PTSD includes cognitive-behavioral therapy, group psychotherapy, and medications such as Clonazepam, Lorazepam and selective
25 serotonin-reuptake inhibitors such as Fluoxetine, Sertraline, Paroxetine, Citalopram and Fluvoxamine. These medications help control anxiety as well as depression. Various forms of exposure therapy (such as systemic desensitization and imaginal flooding) have all been used with PTSD patients. Exposure treatment for PTSD involves repeated reliving of the trauma, under controlled conditions, with the aim of
30 facilitating the processing of the trauma. Therefore, there is a need for better pharmaceutical agents to treat post traumatic stress disorder.

Mood and affective disorders fall within a large group of diseases, including monopolar depression and bi-polar mood disorder. These diseases are treated with

three major classes of compounds. The first group is the heterocyclic antidepressant (HCA's). This group includes the well-known tricyclic antidepressants. The second group of compounds used to treat mood disorders is the monoamine oxidase inhibitors (MAOI's) that are used in particular types of diseases. The third drug is lithium.

- 5 Common side effects from HCA's are sedation and weight gain. In elderly patients with organic brain disease, the side effects of HCA's can also include seizures and behavioral symptoms. The main side effects from using MAOI's occur from dietary and drug interactions. Benign side effects from the use of lithium include, but are not limited to, weight gain, nausea, diarrhea, polyuria, polydipsia, and tremor. Toxic side
10 effects from lithium can include persistent headache, mental confusion, and may reach seizures and cardiac arrhythmias. Therefore, agents with less side effects or interactions with food or other medications would be useful.

- Borderline personality disorder, although not as well known as bipolar disorder, is more common. People having borderline personality disorder suffer from
15 a disorder of emotion regulation. Pharmaceutical agents are used to treat specific symptoms, such as depression or thinking distortions.

- Acquired immune deficiency syndrome (AIDS) results from an infection with the human immunodeficiency virus (HIV). This virus attacks selected cells and impairs the proper function of the immune, nervous, and other systems. HIV infection
20 can cause other problems such as, but not limited to, difficulties in thinking, otherwise known as AIDS dementia complex. Therefore, there is a need to drugs to relieve the confusion and mental decline of persons with AIDS.

- Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, belongs to a class of disorders known as motor neuron diseases wherein specific nerve cells in
25 the brain and spinal cord gradually degenerate to negatively affect the control of voluntary movement. Currently, there is no cure for amyotrophic lateral sclerosis although patients may receive treatment from some of their symptoms and although Riluzole has been shown to prolong the survival of patients. Therefore, there is a need for a pharmaceutical agent to treat this disease.

- 30 Traumatic brain injury occurs when the brain is damaged from a sudden physical assault on the head. Symptoms of the traumatic brain injury include confusion and other cognitive problems. Therefore, there is a need to address the symptoms of confusion and other cognitive problems.

Brain tumors are abnormal growths of tissue found inside of the skull. Symptoms of brain tumors include behavioral and cognitive problems. Surgery, radiation, and chemotherapy are used to treat the tumor, but other agents are necessary to address associated symptoms. Therefore, there is a need to address the symptoms
5 of behavioral and cognitive problems.

Persons with Down's syndrome have in all or at least some of their cells an extra, critical portion of the number 21 chromosome. Adults who have Down's syndrome are known to be at risk for Alzheimer-type dementia. Currently, there is no proven treatment for Down's syndrome. Therefore, there is a need to address the
10 dementia associated with Down's syndrome.

Genetically programmed degeneration of neurons in certain areas of the brain cause Huntington's disease. Early symptoms of Huntington's disease include mood swings, or trouble learning new things or remembering a fact. Most drugs used to treat the symptoms of Huntington's disease have side effects such as fatigue,
15 restlessness, or hyperexcitability. Currently, there is no treatment to stop or reverse the progression of Huntington's disease. Therefore, there is a need of a pharmaceutical agent to address the symptoms with fewer side effects.

Dementia with Lewy Bodies is a neurodegenerative disorder involving abnormal structures known as Lewy bodies found in certain areas of the brain.
20 Symptoms of dementia with Lewy bodies include, but are not limited to, fluctuating cognitive impairment with episodic delirium. Currently, treatment concerns addressing the parkinsonian and psychiatric symptoms. However, medicine to control tremors or loss of muscle movement may actually accentuate the underlying disease of dementia with Lewy bodies. Therefore, there is a need of a pharmaceutical agent to
25 treat dementia with Lewy bodies.

Parkinson's disease is a neurological disorder characterized by tremor, hypokinesia, and muscular rigidity. Currently, there is no treatment to stop the progression of the disease. Therefore, there is a need of a pharmaceutical agent to address Parkinson's.

30 Tardive dyskinesia is associated with the use of conventional antipsychotic drugs. This disease is characterized by involuntary movements most often manifested by puckering of the lips and tongue and/or writhing of the arms or legs. The incidence of tardive dyskinesia is about 5% per year of drug exposure among patients taking

conventional antipsychotic drugs. In about 2% of persons with the disease, tardive dyskinesia is severely disfiguring. Currently, there is no generalized treatment for tardive dyskinesia. Furthermore, the removal of the effect-causing drugs is not always an option due to underlying problems. Therefore, there is a need for a pharmaceutical agent to address the symptoms of tardive dyskinesia.

Pick's disease results from a slowly progressive deterioration of social skills and changes in personality with the resulting symptoms being impairment of intellect, memory, and language. Common symptoms include memory loss, lack of spontaneity, difficulty in thinking or concentrating, and speech disturbances.

Currently, there is no specific treatment or cure for Pick's disease but some symptoms can be treated with cholinergic and serotonin-boosting antidepressants. In addition, antipsychotic medications may alleviate symptoms in FTD patients who are experiencing delusions or hallucinations. Therefore, there is a need for a pharmaceutical agent to treat the progressive deterioration of social skills and changes in personality and to address the symptoms with fewer side effects.

Dysregulation of food intake associated with eating disease, including bulimia nervosa and anorexia nervosa, involve neurophysiological pathways. Anorexia nervosa is hard to treat due to patients not entering or remaining in after entering programs. Currently, there is no effective treatment for persons suffering from severe anorexia nervosa. Cognitive behavioral therapy has helped patients suffering from bulimia nervosa; however, the response rate is only about 50% and current treatment does not adequately address emotional regulation. Therefore, there is a need for pharmaceutical agents to address neurophysiological problems underlying diseases of dysregulation of food intake.

Cigarette smoking has been recognized as a major public health problem for a long time. However, in spite of the public awareness of health hazard, the smoking habit remains extraordinarily persistent and difficult to break. There are many treatment methods available, and yet people continue to smoke. Administration of nicotine transdermally, or in a chewing gum base is common treatments. However, nicotine has a large number of actions in the body, and thus can have many side effects. It is clear that there is both a need and a demand of long standing for a convenient and relatively easy method for aiding smokers in reducing or eliminating

cigarette consumption. A drug that could selectively stimulate only certain of the nicotinic receptors would be useful in smoke cessation programs.

Smoke cessation programs may involve oral dosing of the drug of choice. The drug may be in the form of tablets. However, it is preferred to administer the daily
5 dose over the waking hours, by administration of a series of incremental doses during the day. The preferred method of such administration is a slowly dissolving lozenge, troche, or chewing gum, in which the drug is dispersed. Another drug in treating nicotine addiction is Zyban. This is not a nicotine replacement, as are the gum and patch. Rather, this works on other areas of the brain, and its effectiveness is to help
10 control nicotine craving or thoughts about cigarette use in people trying to quit. Zyban is not very effective and effective drugs are needed to assist smokers in their desire to stop smoking. These drugs may be administered transdermally through the use of skin patches. In certain cases, the drugs may be administered by subcutaneous injection, especially if sustained release formulations are used.

15 Drug use and dependence is a complex phenomenon, which cannot be encapsulated within a single definition. Different drugs have different effects, and therefore different types of dependence. Drug dependence has two basic causes, that is, tolerance and physical dependence. Tolerance exists when the user must take progressively larger doses to produce the effect originally achieved with smaller
20 doses. Physical dependence exists when the user has developed a state of physiologic adaptation to a drug, and there is a withdrawal (abstinence) syndrome when the drug is no longer taken. A withdrawal syndrome can occur either when the drug is discontinued or when an antagonist displaces the drug from its binding site on cell receptors, thereby counteracting its effect. Drug dependence does not always require
25 physical dependence.

In addition drug dependence often involves psychological dependence, that is, a feeling of pleasure or satisfaction when taking the drug. These feelings lead the user to repeat the drug experience or to avoid the displeasure of being deprived of the drug. Drugs that produce strong physical dependence, such as nicotine, heroin and alcohol
30 are often abused, and the pattern of dependence is difficult to break. Drugs that produce dependence act on the CNS and generally reduce anxiety and tension; produce elation, euphoria, or other pleasurable mood changes; provide the user feelings of increased mental and physical ability; or alter sensory perception in some

pleasurable manner. Among the drugs that are commonly abused are ethyl alcohol, opioids, anxiolytics, hypnotics, cannabis (marijuana), cocaine, amphetamines, and hallucinogens. The current treatment for drug-addicted people often involves a combination of behavioral therapies and medications. Medications, such as
5 methadone or LAAM (levo-alpha-acetyl-methadol), are effective in suppressing the withdrawal symptoms and drug craving associated with narcotic addiction, thus reducing illicit drug use and improving the chances of the individual remaining in treatment. The primary medically assisted withdrawal method for narcotic addiction is to switch the patient to a comparable drug that produces milder withdrawal
10 symptoms, and then gradually taper off the substitute medication. The medication used most often is methadone, taken orally once a day. Patients are started on the lowest dose that prevents the more severe signs of withdrawal and then the dose is gradually reduced. Substitutes can be used also for withdrawal from sedatives. Patients can be switched to long-acting sedatives, such as diazepam or phenobarbital,
15 which are then gradually reduced.

Gilles de la Tourette's Syndrome is an inherited neurological disorder. The disorder is characterized by uncontrollable vocal sounds called tics and involuntary movements. The symptoms generally manifest in an individual before the person is 18 years of age. The movement disorder may begin with simple tics that progress to
20 multiple complex tics, including respiratory and vocal ones. Vocal tics may begin as grunting or barking noises and evolve into compulsive utterances. Coprolalia (involuntary scatologic utterances) occurs in 50% of patients. Severe tics and coprolalia may be physically and socially disabling. Tics tend to be more complex than myoclonus, but less flowing than choreic movements, from which they must be
25 differentiated. The patient may voluntarily suppress them for seconds or minutes.

Currently simple tics are often treated with benzodiazepines. For simple and complex tics, Clonidine may be used. Long-term use of Clonidine does not cause tardive dyskinesia; its limiting adverse effect is hypotension. In more severe cases, antipsychotics, such as Haloperidol may be required, but side effects of dysphoria,
30 parkinsonism, akathisia, and tardive dyskinesia may limit use of such antipsychotics. There is a need for safe and effective methods for treating this syndrome.

Age-related macular degeneration (AMD) is a common eye disease of the macula which is a tiny area in the retina that helps produce sharp, central vision

required for "straight ahead" activities that include reading and driving. Persons with AMD lose their clear, central vision. AMD takes two forms: wet and dry. In dry AMD, there is a slow breakdown of light-sensing cells in the macula. There currently is no cure for dry AMD. In wet AMD, new, fragile blood vessels growing beneath the macula as dry AMD worsens and these vessels often leak blood and fluid to cause rapid damage to the macula quickly leading to the loss of central vision. Laser surgery can treat some cases of wet AMD. Therefore, there is a need of a pharmaceutical agent to address AMD.

Glaucoma is within a group of diseases occurs from an increase in intraocular pressure causing pathological changes in the optical disk and negatively affects the field of vision. Medicaments to treat glaucoma either decrease the amount of fluid entering the eye or increase drainage of fluids from the eye in order to decrease intraocular pressure. However, current drugs have drawbacks such as not working over time or causing side effects so the eye-care professional has to either prescribe other drugs or modify the prescription of the drug being used. There is a need for safe and effective methods for treating problems manifesting into glaucoma.

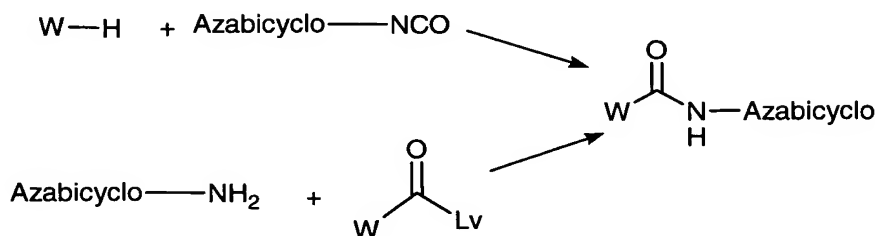
Ischemic periods in glaucoma cause release of excitotoxic amino acids and stimulate inducible form of nitric oxide synthase (iNOS) leading to neurodegeneration. Alpha 7 nicotinic agonists may stimulate the release of inhibitory amino acids such as GABA which will dampen hyperexcitability. Alpha 7 nicotinic agonists are also directly neuroprotective on neuronal cell bodies. Thus alpha 7 nicotinic agonists have the potential to be neuroprotective in glaucoma.

Persons afflicted with pain often have what is referred to as the "terrible triad" of suffering from the pain, resulting in sleeplessness and sadness, all of which are hard on the afflicted individual and that individual's family. Pain can manifest itself in various forms, including, but not limited to, headaches of all severity, back pain, neurogenic, and pain from other ailments such as arthritis and cancer from its existence or from therapy to irradicate it. Pain can be either chronic (persistent pain for months or years) or acute (short-lived, immediate pain to inform the person of possible injury and need of treatment). Persons suffering from pain respond differently to individual therapies with varying degrees of success. There is a need for safe and effective methods for treating pain.

Finally, the compounds of the present invention may be used in combination therapy with typical and atypical anti-psychotic drugs. All compounds within the present invention are useful for and may also be used in combination with each other to prepare pharmaceutical compositions. Such combination therapy lowers the effective dose of the anti-psychotic drug and thereby reduces the side effects of the anti-psychotic drugs. Some typical anti-psychotic drugs that may be used in the practice of the invention include Haldol. Some atypical anti-psychotic drugs include Ziprasidone, Olanzapine, Risperidone, and Quetiapine.

Compounds of Formula I can be prepared as shown in Scheme 1. The key step in the preparation of this class of compounds is the coupling of an amino-azabicyclic moiety with the requisite acid chloride (Lv = Cl), aryl carbamate (e.g., Lv = phenyl, p-NO₂-phenyl), carbonyl imidazole or carboxylic acid (Lv = OH) in the presence of an activating reagent using procedures described in *J. Org. Chem.* **1987**, 52, 2319, *Tetrahedron Lett.* **1999**, 40, 2733 and *J. Med. Chem.* **1985**, 28, 1346. Suitable activating reagents are well known in the art, for examples see Kiso, Y.; Yajima, H. "Peptides" pp. 39-91, San Diego, CA, Academic Press, (1995), and include, but are not limited to, agents such as a carbodiimides, phosphonium and uronium salts (such as uronium salt HATU). Alternatively, heterocycles W-H can be reacted with azabicyclo isocyanates using procedures described in *Synlett* **1995**, 605. Methods to prepare azabicyclo isocyanates are known to one of ordinary skill in the art (see EP 550007).

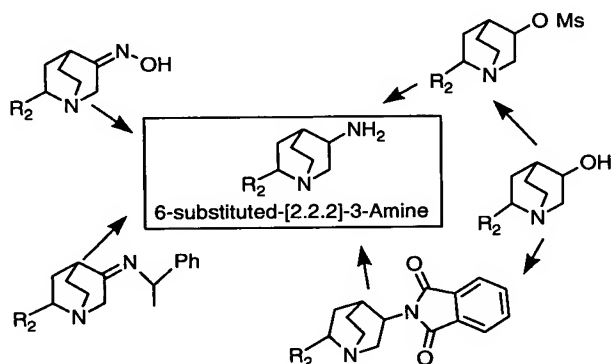
Scheme 1



One of ordinary skill in the art will recognize that the methods described for the reaction of the unsubstituted 3-aminoquinuclidine (R₂ is absent) are equally applicable to substituted compounds (R₂ is present). Certain 6-substituted-[2.2.2]-3-amines (Azabicyclo I) are known in the art. The preparation of compounds where R₂ is at C-6 of the quinuclidine and is other than H is described in *Acta Pol. Pharm.*

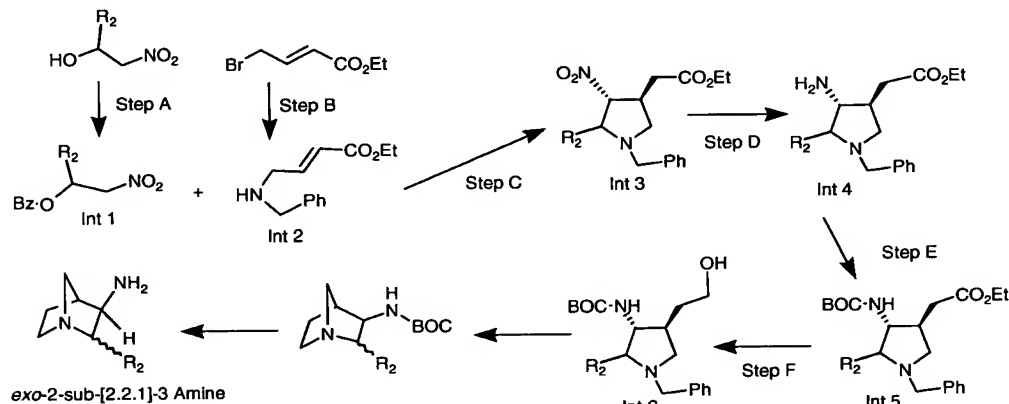
1981, 179. Certain 2-substituted-[2.2.2]-3-amines (Azabicyclo I) are known in the art. The preparation of compounds where R₂ is at C-2 of the quinuclidine and is other than H is described in *J. Med. Chem.* **1975**, 18, 587.

Alternatively, there are several methods by which the amine precursor for
 5 Azabicyclo I where R₂ is other than H can be obtained. Although the scheme depicted below is for compounds where R₂ is at the C-6 position of the quinuclidine, one of ordinary skill in the art would be able to obtain the quinuclidine with substitution at C-2 also. The substituted-[2.2.2]-3-amine can be prepared by reduction of an oxime or an imine of the corresponding substituted-3-quinuclidinone by methods known to
 10 one of ordinary skill in the art (see *J. Labelled Compds. Radiopharm.* **1995**, 53; *J. Med. Chem.* **1998**, 988; *Synth. Commun.* **1992**, 1895; *Synth. Commun.* **1996**, 2009). Alternatively, the substituted-[2.2.2]-3-amine can be prepared from a substituted-3-hydroxyquinuclidine by Mitsunobu reaction followed by deprotection as described in *Synth. Commun.* **1995**, 1895. Alternatively, the substituted-[2.2.2]-3-amine can be
 15 prepared by conversion of a substituted-3-hydroxyquinuclidine into the corresponding mesylate or tosylate, followed by displacement with sodium azide and reduction as described in *J. Med. Chem.* **1975**, 587.

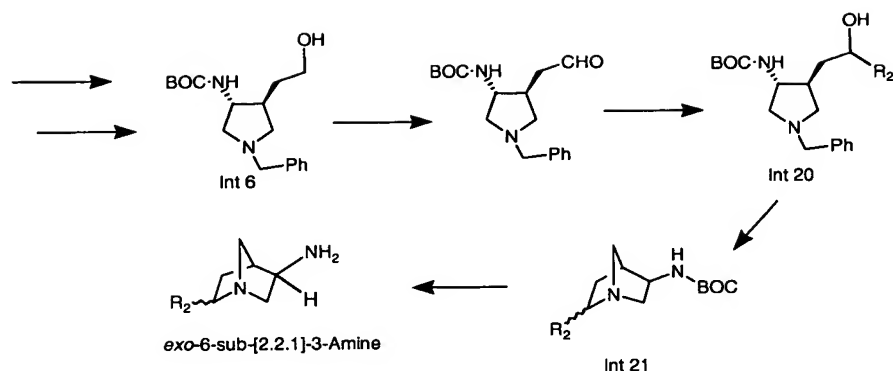


The 2-substituted-3-quinuclidinones, where R₂ is substituted alkyl, cycloalkyl,
 20 or can be prepared by known procedures (see *Tett. Lett.* **1972**, 1015; *J. Am. Chem. Soc.* **1994**, 1278; *J. Am. Chem. Soc.* **1989**, 4548; *Tetrahedron*, **2000**, 1139). The 2-substituted-3-quinuclidinones, where R₂ is aryl, can be prepared by palladium catalyzed arylation as described in *J. Am. Chem. Soc.* **1999**, 1473 and *J. Am. Chem. Soc.* **2000**, 1360. The 6-substituted-3-quinuclidinones can be prepared by known
 25 procedures (see *J. Gen. Chem. Russia* **1963**, 3791, *J. Chem. Soc. Perkin Trans. I* **1991**, 409, *J. Org. Chem.* **2000**, 3982).

One of ordinary skill in the art will recognize that the methods described for the reaction of the unsubstituted 3-amino-1-azabicyclo[2.2.1]heptane ($R_2=H$) are equally applicable to substituted compounds ($R_2 \neq H$). For where Azabicyclo II has substitution at C-2, compounds can be prepared from appropriately substituted nitro alcohols using procedures described in *Tetrahedron* (1997), 53, p. 11121 as shown below. Methods to synthesize nitro alcohols are well known in the art (see *J. Am. Chem. Soc.* (1947), 69, p 2608). The scheme below is a modification of the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt, described in detail herein, to show how to obtain these amine precursors. The desired salt can be made using standard procedures.



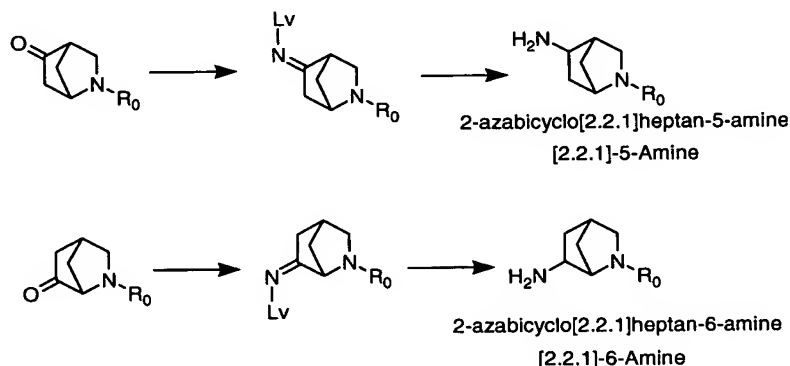
For Azabicyclo II where R_2 is other than H at the C-6 position, compounds can also be prepared by modification of intermediates described in the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt, described in detail herein. For example, Int 6 can be oxidized to the aldehyde and treated with an organometallic reagent to provide Int 20 using procedures described in *Tetrahedron* (1999), 55, p 13899. Int 20 can be converted into the amine using methods described for the synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro para-toluenesulfonate) salt. Once the amine is obtained, the desired salt can be made using standard procedures.



The schemes used are for making *exo*-3-amino-1-azabicyclo[2.2.1]heptane. However, the modifications discussed are applicable to make the *endo* isomer also.

One of ordinary skill in the art will also recognize that the methods described for the reaction of the unsubstituted 1-azabicyclo[3.2.1]octan-3-amine or 1-azabicyclo[3.2.2]nonan-3-amine ($R_2=H$) are equally applicable to substituted compounds ($R_2 \neq H$). The R_2 substituent may be introduced as known to one skilled in the art through standard alkylation chemistry. Exposure of 1-azabicyclo[3.2.1]octan-3-one or 1-azabicyclo[3.2.2]nonan-3-one to a hindered base such as LDA (lithium diisopropylamide) in a solvent such as THF or ether between 0°C to -78°C followed by the addition of an alkylating agent ($R_2\text{Lv}$, where $\text{Lv} = \text{Cl}, \text{Br}, \text{I}, \text{OTs}, \text{etc.}$) will, after being allowed to warm to about 0°C to rt followed by an aqueous workup, provide the desired compound as a mixture of isomers. Chromatographic resolution (flash, HPLC, or chiral HPLC) will provided the desired purified alkylated ketones. From there, formation of the oxime and subsequent reduction will provide the desired stereoisomers.

N-(2-azabicyclo[2.2.1]hept)-5-amine and 6-amine:



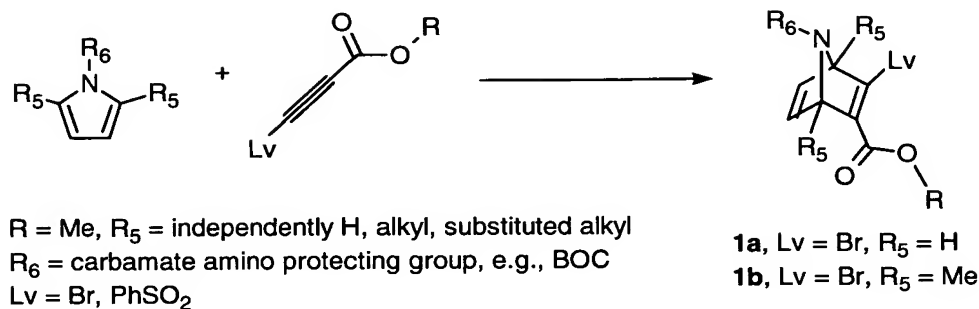
where Lv can be -CH₂Ph, -CH(Me)Ph, -OH, -OMe, or -OCH₂Ph.

The respective amine precursors for Azabicyclo V and Azabicyclo VI can be prepared by reduction of an oxime or an imine of the corresponding *N*-2-azabicyclo[2.2.1]-heptanone by methods known to one skilled in the art (see *J. Labelled Compds. Radiopharm.*, 53-60 (1995), *J. Med. Chem.* 988-995, (1998), *Synth. Commun.* 1895-1911 (1992), *Synth. Commun.* 2009-2015 (1996)). The oximes can be prepared by treatment of the *N*-2-azabicyclo[2.2.1]heptanones with hydroxylamine hydrochloride in the presence of a base. The imines can be prepared by treatment of the *N*-2-azabicyclo[2.2.1]-heptanones with a primary amine under dehydrating conditions. The *N*-2-azabicyclo[2.2.1]heptanones can be prepared by known procedures (see *Tet. Lett.* 1419-1422 (1999), *J. Med. Chem.* 2184-2191 (1992), *J. Med. Chem.* 706-720 (2000), *J. Org. Chem.*, 4602-4616 (1995)).

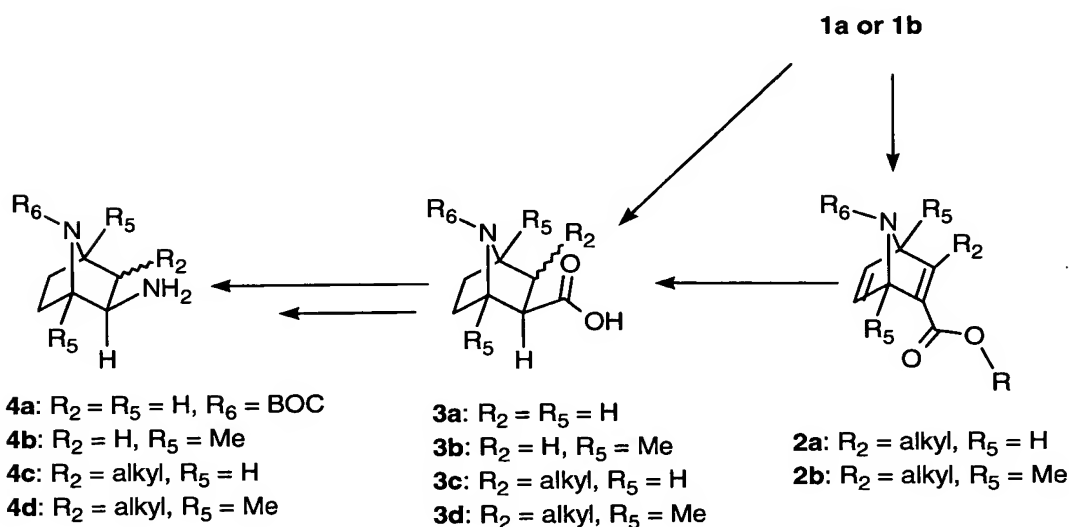
There are various methods for the construction of the optionally substituted 7-azabicyclo[2.2.1]heptane ring system. For example, the independent work of Trudell (*R*₅ = H, Zhang, C., Trudell, M.L., *J. Org. Chem.*, 61, 7189-7191, **1996**), and Schultz (*R*₅ = Me, Schultz, A.G., Shen, M.S., *Tetrahedron Lett.*, 22, 3347-3350, **1981**) describes the utility of a Diels-Alder approach toward preparing this ring system with functionality suitable for further elaboration to the desired 2-amino-7-azabicyclo[2.2.1]heptane (Scheme 2). For instance, Trudell reports (Zhang, C., Trudell, M.L., *Tetrahedron*, 54, 8349-8354, **1998**) that Diels-Alder adduct **1a** (where *R*₆ = methylcarbamate, *R*₅ = H, and Lv = Br) could readily be functionalized at C-3 via reaction with organocopper species to introduce the substituent *R*₂ in **2a,b**. Likewise, hydrogenolysis of adduct **1a,b** or **2a,b** followed by isomerization of the *endo* products as described by Singh (Singh, S., Basmadjian, G.P., *Tetrahedron Lett.*, 38, 6829-6830, **1997**) could provide access to the required *exo* acid **3a-d**. Treatment of **3** with diphenylphosphoryl azide in the presence of a tertiary amine base (e.g., Et₃N) in a suitable solvent such as toluene, followed by warming of the intermediate acylazide in the presence of a suitable alcohol (e.g., benzyl alcohol) would effect the well-known Curtius rearrangement to provide a differentially protected *bis* carbamate which could be cleaved under typical hydrogenolysis conditions (e.g., 10% Pd/C, EtOH, H₂, ambient to 50 psi) to give the desired amine **4**. Alternatively, the differentially protected *bis* carbamate might provide an attractive point of intervention for the

chromatographic resolution of the individual 2-*exo* isomers prior to cleavage to amine
4.

Scheme 2



5



In the case where R₆ = *tert*-butoxycarbonyl, deprotection of the 7-aza group
can be conveniently accomplished under acidic conditions in a suitable solvent such
as methanol. After deprotection, the secondary amine may be functionalized with
alkyl and substituted alkyl via reductive amination or alkylative procedures.

It will be apparent to those skilled in the art that the requisite carboxylic acids
or carboxylic acid equivalents can be obtained through synthesis via literature
procedures or through the slight modification thereof. For example, methods to
prepare carboxylic acids or carboxylic acid equivalents starting from pyrroles or
pyrazoles are known to one of ordinary skill in the art (see *J. Org. Chem.* **1987**, 52,
2319, *Tetrahedron Lett.* **1999**, 40, 2733 and Greene, T. W. and Wuts, P. G. M.
"Protective Groups in Organic Synthesis", 3rd Edition, p. 549, New York:Wiley,

(1999)). Several pyrroles and pyrazoles of the Formula W-H are commercially available or can be obtained by methods described in *Synthesis* **1997**, 563, *J. Org. Chem.* **1997**, 62, 2649, *J. Heterocyclic Chem.* **1993**, 30, 865, *Monatsh. Chem.* **1993**, 124, 199, *J. Heterocyclic Chem.* **1993**, 30, 865, *J. Org. Chem.* **1992**, 57, 1653, *J. Org. Chem.* **1990**, 55, 6317, *J. Org. Chem.* **1984**, 49, 3239, *Tetrahedron Lett.* **1983**, 24, 3455, and *Heterocycles* **1982**, 19, 1223.

Treatment of the carboxamide with a sulfurating agent such as Lawesson's Reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in, for instance, dioxane at an appropriate temperature provides the corresponding thioamide, e.g., X in formula I is S. See Lawesson et. al. in *Bull. Soc. Chim. Belg.*, 229 (1978)), or P₄S₁₀ (see *Chem. Rev.*, 45 (1961). Alternatively, one can react a dithiocarboxylic ester with the corresponding azbicyclo moiety to form the same thioamide.

AMINES

Preparation of *N*-(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride (2*S*-methyl-2.2.2-Amine):

Preparation of 2-methylquinuclidin-3-one.

A mixture of 2-methylene-3-quinuclidinone dihydrate hydrochloride (27.2g, 0.13 mol, 1eq) and K₂CO₃ (86.0g, 0.62 mol, 4.8eq) is dissolved in 130mL water and 250mL CH₂Cl₂ and stirred vigorously. After 3 days, the layers are separated and the aqueous layer is extracted with CH₂Cl₂. The combined organic layers are dried (MgSO₄), filtered and concentrated to give 17.8g (100%) of 2-methylenequinuclidin-3-one as a yellow oil. MS (ESI) for C₈H₁₁NO *m/z* 138.1 (M⁺).

Preparation of 2-methylquinuclidin-3-one.

2-Methylenequinuclidin-3-one (17.8g, 0.13 mol, 1eq) is dissolved in 40mL MeOH in a Parr hydrogenation bottle. A THF slurry of 10% Pd/C (0.57g) is added. The mixture is hydrogenated for 45 min at 45 psi, recharging as needed. The mixture is filtered through a pad of Celite. The Celite is washed with excess MeOH. The solution is concentrated to give a solid and a yellow oil. The mixture is taken up in ether, filtered and concentrated to provide 16.2g (90%) of 2-methylquinuclidin-3-one. MS (ESI) for C₈H₁₃NO *m/z* 140.2 (M⁺).

Preparation of (3*E/Z*)-2-methyl-1-azabicyclo[2.2.2]octan-3-one oxime hydrochloride.

2-Methylquinuclidin-3-one (39.6g, 0.28 mol, 1eq) and hydroxylamine
 5 hydrochloride (20.0g, 0.29 mol, 1.01eq) are dissolved in 170mL absolute EtOH. The mixture is heated under reflux until a clear solution develops (about 20 min), after which is immediately followed by formation of a white precipitate. The reaction is cooled and allowed to stand overnight. The mixture is cooled in an ice bath, the solids are filtered and dried (house vacuum) to provide 46.4g of (3*E/Z*)-2-methyl-1-
 10 azabicyclo[2.2.2]octan-3-one oxime hydrochloride. A second crop of 2.4g is also obtained. Overall yield is 48.8g (90%). The 2-methyl-1-azabicyclo[2.2.2]octan-3-one oxime hydrochloride is a 4:1 mixture of oxime isomers. MS (ESI) for C₈H₁₄N₂O *m/z* 154.8 (M⁺). Partial ¹H NMR (400 MHz, DMSO) δ 4.39 (0.2H), 4.29 (0.8H), 1.57 (0.6H), 1.47 (2.4H).

15

A solution of sodium *n*-propoxide (prepared from 5.5g sodium (0.24mol) and 100mL *n*-propanol) is added dropwise to a suspension of (3*E/Z*)-2-methyl-1-azabicyclo[2.2.2]octan-3-one oxime hydrochloride (45.8g, 0.24mol, 1eq) in 150 mL *n*-propanol. After complete addition, 250mL of *n*-propanol is added, and the mixture
 20 is heated under reflux. Sodium (55.2g, 2.40mol, 10 eq) is added in portions to the refluxing mixture. The mixture is heated under reflux overnight. After about 14h, the mixture is cooled, water is added and the layers are separated. The *n*-propanol layer is washed with brine and dried (MgSO₄). The combined aqueous layers are extracted with CHCl₃ and dried (MgSO₄). The combined, dried organic layers are treated with
 25 about 70mL concentrated HCl. The solvent is removed *in vacuo*. Absolute EtOH is added, and the solvent is removed. The sequence is repeated 2-3 times with fresh EtOH until a white solid formed. Absolute EtOH is added, the solids are filtered and dried (vacuum oven, about 60°C) to provide 36.5g of *trans* 3-amino-2-methylquinuclidine dihydrochloride. MS (ESI) for C₈H₁₆N₂ *m/z* 141.3 (M⁺).
 30 Additional material is obtained from the mother liquor: 7.8g (2nd crop) and 1.5g (3rd crop); this material is a mixture of both *trans* and *cis* isomers.

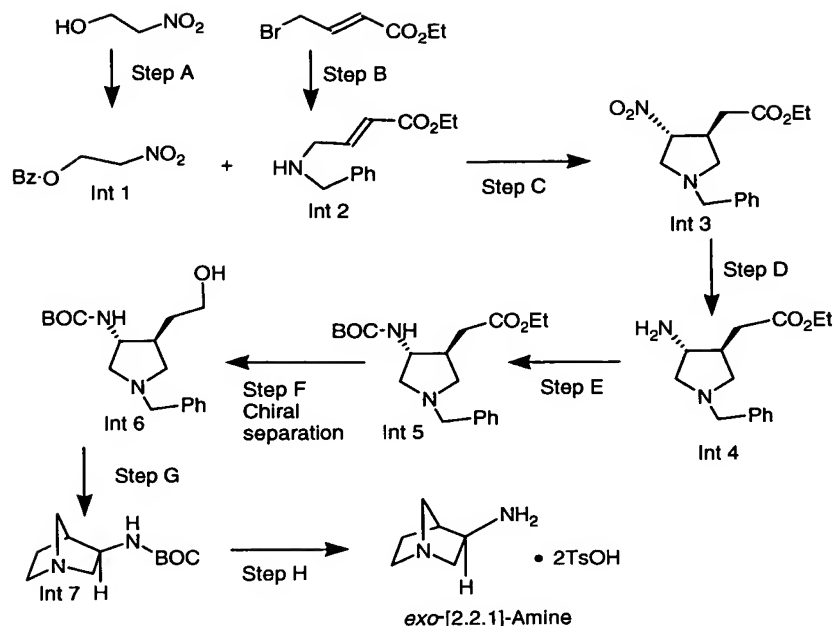
4-Chlorobenzoic acid (26.3g, 0.17 mol, 1.1eq) and TEA (106mL, 0.76 mol, 5 eq) are dissolved in 300mL THF. Diphenylphosphoryl chloride (32.0mL, 0.1681mol,

1.1 eq) is added dropwise. After 1h, *trans* 2-methylquinuclidin-3-amine dihydrochloride (32.6g, 0.15 mol, 1 eq) is added. The mixture is allowed to stir at RT overnight. 1N NaOH (about 100mL) is added, and the pH is adjusted to pH 11 with 50% NaOH and about 50g K₂CO₃. The layers are separated. The aqueous layer is
 5 extracted with CHCl₃. The combined organic layers are dried (MgSO₄), filtered and concentrated. The residue is taken up in heptane and concentrated to give 35.1g (82%) of 4-chloro-*N*-(2-methyl-1-azabicyclo[2.2.2]oct-3-yl)phenyl-2-carboxamide as a light yellow solid. The enantiomers are separated on a 5 x 50 cm Chiralcel OD column at 30°C, eluting with 15% IPA/heptane + 0.1% DEA at 90mL/min to provide
 10 17.4g of 4-chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]benzamide at about 97% ee. The p-TsOH salt is prepared and recrystallized from EtOH/EtOAc. $[\alpha]_D^{25} = +3^\circ$ (c 0.96, methanol). HRMS (FAB) calcd for C₁₅H₁₉ClN₂O + H 279.1264, found 279.1272.

A solution of 4-chloro-*N*-[(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]oct-3-yl]benzamide (17.2g, 61.7mmol) in absolute EtOH (70mL) and concentrated HCl (70mL) is heated under reflux for about 64h. The reaction is monitored for disappearance of starting amide by reverse phase HPLC (ZORBAX Eclipse XDB-C8, 4.6mm x 15cm, 80:12:8 H₂O/CH₃CN/IPA). The solvent is removed *in vacuo*. The residue is dissolved/suspended in EtOH and the solvent is removed (twice). The solid
 20 is suspended in boiling EtOH, filtered and dried (vacuum oven, about 60°C) to provide 8.8g (67%) of *N*-(2*S*,3*R*)-2-methyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride as a white solid. MS (EI) *m/z* 141.2 (M⁺).

Preparation of the 1-azabicyclo-2.2.1 Amines:

25 Synthesis of *exo*-3-amino-1-azabicyclo[2.2.1]heptane
 as the bis(hydro para-toluenesulfonate) salt (*exo*-[2.2.1]-Amine):



Step A. Preparation of 2-(benzoyloxy)-1-nitroethane (Int 1).

Benzoyl chloride (14.9 mL, 128 mmol) is added to a stirred solution of nitroethanol (9.2 mL, 128 mmol) in dry benzene (120 mL). The solution is refluxed for 24 hr and then concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (80:20) affords Int 1 as a white solid (68% yield): ^1H NMR (CDCl_3) δ 8.0, 7.6, 7.4, 4.9, 4.8.

Step B. Preparation of ethyl E-4-(benzylamino)-2-butenate (Int 2).

Ethyl E-4-bromo-2-butenate (10 mL, 56 mmol, tech grade) is added to a stirred solution of benzylamine (16 mL, 146 mmol) in CH_2Cl_2 (200 mL) at rt. The reaction mixture stirs for 15 min, and is diluted with ether (1 L). The mixture is washed with saturated aqueous NaHCO_3 solution (3x) and water, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (70:30) affords Int 2 as a clear oil (62% yield): ^1H NMR (CDCl_3) δ 7.4-7.2, 7.0, 6.0, 4.2, 3.8, 3.4, 2.1-1.8, 1.3.

Step C. Preparation of *trans*-4-nitro-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 3).

A solution of Int 1 (6.81 g, 34.9 mmol) and Int 2 (7.65 g, 34.9 mmol) in EtOH (70 mL) stirs at rt for 15 h and is then concentrated *in vacuo*. The residue is diluted with ether (100 mL) and saturated aqueous NaHCO_3 solution (100 mL). The organic

layer is separated and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-EtOAc (85:15) affords Int 3 as a clear oil (76% yield): ^1H NMR (CDCl_3) δ 7.4-7.3, 4.8-4.7, 4.1, 3.8-3.6, 3.3-3.0, 2.7-2.6, 2.4-2.3, 1.2.

5

Step D. Preparation of *trans*-4-amino-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 4).

A mixture of Int 3 (3.28 g, 11.2 mmol) and RaNi (1.5 g) in EtOH (100 mL) is placed in a Parr bottle and hydrogenated for 4 h under an atmosphere of hydrogen (46
10 psi) at rt. The mixture is filtered through a pad of Celite, and the solvent is removed *in vacuo* to afford Int 4 as a clear oil (100% yield): ^1H NMR (300 MHz, CDCl_3) δ 7.3-7.2, 4.1, 3.6, 3.2, 3.0-2.9, 2.8, 2.8-2.6, 2.6-2.4, 2.30-2.2, 1.2.

Step E. Preparation of *trans*-4-(1,1-dimethylethoxycarbonylamido)-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester (Int 5).
15

Di-*tert*-butyldicarbonate (3.67 g, 16.8 mmol) is added to a stirred solution of Int 4 (2.94 g, 11.2 mmol) in CH_2Cl_2 (30 mL) cooled in an ice bath. The reaction is allowed to warm to rt and stirred overnight. The mixture is concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with
20 hexanes-EtOAc (80:20) affords Int 5 as a white solid (77% yield): ^1H NMR (300 MHz, CDCl_3) δ 7.4-7.2, 5.1-4.9, 4.1, 4.0-3.8, 3.6, 3.2-3.0, 2.8-2.6, 2.5-2.4, 2.3-2.1, 1.4, 1.3.

Step F. Preparation of *trans* (*tert*-butoxycarbonylamino)-4-(2-hydroxyethyl)-1-(N-phenylmethyl) pyrrolidine (Int 6).
25

LiAlH_4 powder (627 mg, 16.5 mmol) is added in small portions to a stirred solution of Int 5 (3.0 g, 8.3 mmol) in anhydrous THF (125 mL) in a -5°C bath. The mixture is stirred for 20 min in a -5°C bath, then quenched by the sequential addition of water (0.6 mL), 15% (w/v) aqueous NaOH (0.6 mL) and water (1.8 mL). Excess
30 anhydrous K_2CO_3 is added, and the mixture is stirred for 1 h, then filtered. The filtrate is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel. Elution with EtOAc affords Int 6 as a white solid (94% yield): ^1H NMR (CDCl_3) δ 7.4-7.3, 5.3-5.2, 4.1-4.0, 3.9-3.7, 3.3-3.2, 2.8-2.7, 2.3-2.1, 1.7, 1.5.

Int 6 is a racemic mixture that can be resolved via chromatography using a Diacel chiral pack AD column. From the two enantiomers thus obtained, the (+)-enantiomer, $[\alpha]_D^{25} +35$ (c 1.0, MeOH), gives rise to the corresponding optically pure *exo*-4-*S* final compounds, whereas the (-)-enantiomer, $[\alpha]_D^{25} -34$ (c 0.98, MeOH), gives rise to optically pure *exo*-4-*R* final compounds. The methods described herein use the (+)-enantiomer of Int 6 to obtain the optically pure *exo*-4-*S* final compounds. However, the methods used are equally applicable to the (-)-enantiomer of Int 6, making non-critical changes to the methods provided herein to obtain the optically pure *exo*-4-*R* final compounds.

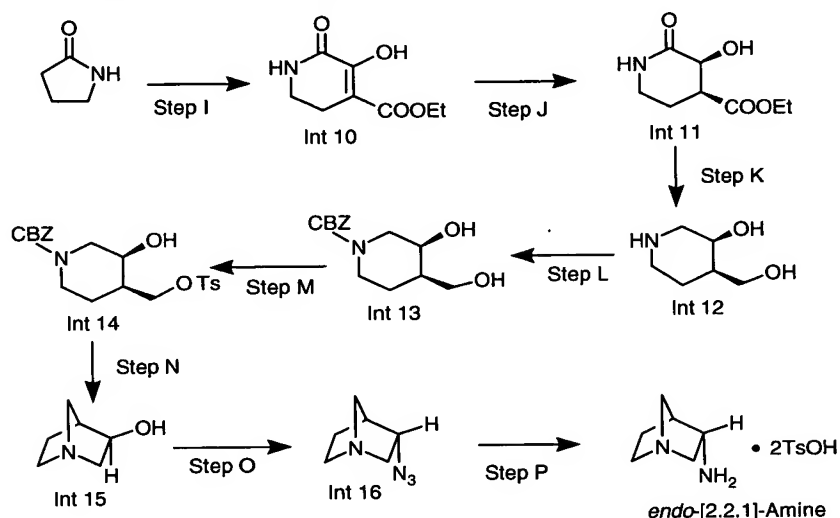
Step G. Preparation of *exo* 3-(*tert*-butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane (Int 7).

TEA (8.0 g, 78.9 mmol) is added to a stirred solution of Int 6 (2.5 g, 7.8 mmol) in CH_2Cl_2 (50 mL), and the reaction is cooled in an ice-water bath. $\text{CH}_3\text{SO}_2\text{Cl}$ (5.5 g, 47.8 mmol) is then added dropwise, and the mixture is stirred for 10 min in an ice-water bath. The resulting yellow mixture is diluted with saturated aqueous NaHCO_3 solution, extracted with CH_2Cl_2 several times until no product remains in the aqueous layer by TLC. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue is dissolved in EtOH (85 mL) and is heated to reflux for 16 h. The reaction mixture is allowed to cool to rt, transferred to a Parr bottle and treated with 10% Pd/C catalyst (1.25 g). The bottle is placed under an atmosphere of hydrogen (53 psi) for 16 h. The mixture is filtered through Celite, and fresh catalyst (10% Pd/C, 1.25 g) is added. Hydrogenolysis continues overnight. The process is repeated three more times until the hydrogenolysis is complete. The final mixture is filtered through Celite and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel. Elution with CHCl_3 -MeOH- NH_4OH (90:9.5:0.5) affords Int 7 as a white solid (46% yield): ^1H NMR (CDCl_3) δ 5.6-5.5, 3.8-3.7, 3.3-3.2, 2.8-2.7, 2.0-1.8, 1.7-1.5, 1.5.

Step H. Preparation of *exo*-3-amino-1-azabicyclo[2.2.1]heptane bis(hydro-*para*-toluenesulfonate).

Para-toluenesulfonic acid monohydrate (1.46 g, 7.68 mmol) is added to a stirred solution of Int 7 (770 mg, 3.63 mmol) in EtOH (50 mL). The reaction mixture is heated to reflux for 10 h, followed by cooling to rt. The precipitate is collected by vacuum filtration and washed with cold EtOH to give *exo*-[2.2.1]-Amine as a white solid (84% yield): ¹H NMR (CD₃OD) δ 7.7, 7.3, 3.9-3.7, 3.7-3.3, 3.2, 2.4, 2.3-2.2, 1.9-1.8.

Synthesis of *endo*-3-amino-1-azabicyclo[2.2.1]heptane as the bis(hydro *para*-toluenesulfonate) salt (*endo*-[2.2.1]-Amine):



Step I. Preparation of ethyl 5-hydroxy-6-oxo-1,2,3,6-tetrahydropyridine-4-carboxylate (Int 10).

Absolute EtOH (92.0 mL, 1.58 mol) is added to a mechanically stirred suspension of potassium ethoxide (33.2 g, 395 mmol) in dry toluene (0.470 L). When the mixture is homogeneous, 2-pyrrolidinone (33.6 g, 395 mmol) is added, and then a solution of diethyl oxalate (53.1 mL, 390 mmol) in toluene (98 mL) is added via an addition funnel. After complete addition, toluene (118 mL) and EtOH (78 mL) are added sequentially. The mixture is heated to reflux for 18 h. The mixture is cooled to rt and aqueous HCl (150 mL of a 6.0 M solution) is added. The mixture is mechanically stirred for 15 min. The aqueous layer is extracted with CH₂Cl₂, and the combined organic layers are dried over MgSO₄, filtered and concentrated *in vacuo* to a yellow residue. The residue is recrystallized from EtOAc to afford Int 10 as a yellow solid (38% yield): ¹H NMR (CDCl₃) δ 11.4, 7.4, 4.3, 3.4, 2.6, 1.3.

Step J. Preparation of ethyl *cis*-3-hydroxy-2-oxopiperidine-4-carboxylate (Int 11).

A mixture of Int 10 (15 g, 81 mmol) and 5% rhodium on carbon (2.0 g) in glacial acetic acid is placed under an atmosphere of hydrogen (52 psi). The mixture is shaken for 72 h. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo* to afford Int 11 as a white solid (98% yield): ¹H NMR (CDCl₃) δ 6.3, 4.2, 4.0-3.8, 3.4, 3.3-3.2, 2.2, 1.3.

Step K. Preparation of *cis*- 4-(hydroxymethyl)piperidin-3-ol (Int 12).

Int 11 (3.7 g, 19.9 mmol) as a solid is added in small portions to a stirred solution of LiAlH₄ in THF (80 mL of a 1.0 M solution) in an ice-water bath. The mixture is warmed to rt, and then the reaction is heated to reflux for 48 h. The mixture is cooled in an ice-water bath before water (3.0 mL, 170 mmol) is added dropwise, followed by the sequential addition of NaOH (3.0 mL of a 15% (w/v) solution) and water (9.0 mL, 500 mmol). Excess K₂CO₃ is added, and the mixture is stirred vigorously for 15 min. The mixture is filtered, and the filtrate is concentrated *in vacuo* to afford Int 12 as a yellow powder (70% yield): ¹H NMR (DMSO-*d*₆) δ 4.3, 4.1, 3.7, 3.5-3.2, 2.9-2.7, 2.5-2.3, 1.5, 1.3.

Step L. Preparation of benzyl *cis*-3-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate (Int 13).

N-(benzyloxy carbonyloxy)succinimide (3.04 g, 12.2 mmol) is added to a stirred solution of Int 12 (1.6 g, 12.2 mmol) in saturated aqueous NaHCO₃ (15 mL) at rt. The mixture is stirred at rt for 18 h. The organic and aqueous layers are separated. The aqueous layer is extracted with ether (3X). The combined organic layers are dried over anhydrous K₂CO₃, filtered and concentrated *in vacuo* to afford Int 13 as a yellow oil (99% yield): ¹H NMR (CDCl₃) δ 7.4-7.3, 5.2, 4.3, 4.1, 3.8-3.7, 3.0-2.8, 2.1, 1.9-1.7, 1.4.

Step M. Preparation of benzyl *cis*-3-hydroxy-4-[(4-methylphenyl)sulfonyl oxymethyl]piperidine-1-carboxylate (Int 14).

Para-toluenesulfonyl chloride (1.0 g, 5.3 mmol) is added to a stirred solution of Int 13 (3.6 g, 5.3 mmol) in pyridine (10 mL) in a -15°C bath. The mixture is stirred

for 4 h, followed by addition of HCl (4.5 mL of a 6.0 M solution). CH₂Cl₂ (5 mL) is added. The organic and aqueous layers are separated. The aqueous layer is extracted with CH₂Cl₂. The combined organic layers are washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford Int 14 as a colorless oil (78% yield): ¹H NMR (CDCl₃) δ 7.8, 7.4-7.2, 5.1, 4.3-4.2, 4.1, 3.9-3.8, 2.9-2.7, 2.4, 1.9, 1.6-1.3.

Step N. Preparation of *exo*-1-azabicyclo[2.2.1]heptan-3-ol (Int 15).

A mixture of Int 14 (3.6 g, 8.6 mmol) and 10% Pd/C catalyst (500 mg) in EtOH (50 mL) is placed under an atmosphere of hydrogen. The mixture is shaken for 16 h. The mixture is filtered through Celite. Solid NaHCO₃ (1.1 g, 13 mmol) is added to the filtrate, and the mixture is heated in an oil bath at 50°C for 5 h. The solvent is removed *in vacuo*. The residue is dissolved in saturated aqueous K₂CO₃ solution. Continuous extraction of the aqueous layer using a liquid-liquid extraction apparatus (18 h), followed by drying the organic layer over anhydrous K₂CO₃ and removal of the solvent *in vacuo* affords Int 15 as a white solid (91% yield): ¹H NMR δ 3.8, 3.0-2.8, 2.6-2.5, 2.4-2.3, 1.7, 1.1.

Step O. Preparation of *endo*-3-azido-1-azabicyclo[2.2.1]heptane (Int 16).

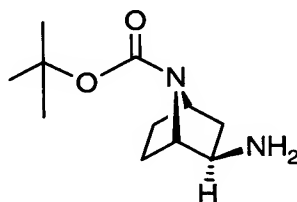
To a mixture of Int 15 (1.0 g, 8.9 mmol) and triphenyl phosphine (3.0 g, 11.5 mmol) in toluene-THF (50 mL, 3:2) in an ice-water bath are added sequentially a solution of hydrazoic acid in toluene (15 mL of ca. 2 M solution) and a solution of diethyl azadicarboxylate (1.8 mL, 11.5 mmol) in toluene (20 mL). The mixture is allowed to warm to rt and stir for 18 h. The mixture is extracted with aqueous 1.0M HCl solution. The aqueous layer is extracted with EtOAc, and the combined organic layers are discarded. The pH of the aqueous layer is adjusted to 9 with 50% aqueous NaOH solution. The aqueous layer is extracted with CH₂Cl₂ (3X), and the combined organic layers are washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel. Elution with CHCl₃-MeOH-NH₄OH (92:7:1) affords Int 16 as a colorless oil (41% yield): ¹H NMR (CDCl₃) δ 4.1, 3.2, 2.8, 2.7-2.5, 2.2, 1.9, 1.5.

Step P. Preparation of *endo*-3-amino-1-azabicyclo[2.2.1]heptane bis(hydro-*para*-toluenesulfonate).

A mixture of Int 16 (250 mg, 1.8 mmol) and 10% Pd/C catalyst (12 mg) in EtOH (10 mL) is placed under an atmosphere of hydrogen (15 psi). The mixture is stirred for 1 h at rt. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo*. The residue is dissolved in EtOH (10 mL) and *para*-toluenesulfonic acid monohydrate (690 mg, 3.7 mmol) is added. The mixture is stirred for 30 min, and the precipitate is filtered. The precipitate is washed sequentially with cold EtOH and ether. The precipitate is dried *in vacuo* to afford *endo*-[2.2.1]-Amine as a white solid (85% yield): ^1H NMR (CD_3OD) δ 7.7, 7.3, 4.2, 3.9, 3.6-3.4, 3.3-3.2, 2.4, 2.3, 2.1.

10

Preparation of *tert*-butyl (1S, 2R, 4R)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate:



Methyl propiolate (52 ml, 0.583 mol) is combined with recrystallized *N*-bromo-succinimide (120 g, 0.674 mol) in 1,700 ml acetone under nitrogen. The solution is treated with silver nitrate (9.9 g, 0.0583 mol) neat in a single lot and the reaction is stirred 6 h at RT. The acetone is removed under reduced pressure (25°C, bath temperature) to provide a gray slurry. The slurry is washed with 2 x 200 ml hexane, the gray solid is removed by filtration, and the filtrate is concentrated *in vacuo* to provide 95 g of a pale yellow oily residue. The crude material is distilled via short path under reduced pressure (65°C, about 25 mm Hg) into a dry ice/acetone cooled receiver to give 83.7 g (88%) of methyl-3-bromo-propiolate as a pale yellow oil. Anal. calc'd for $\text{C}_4\text{H}_3\text{BrO}_2$: C, 29.48; H, 1.86. Found: C, 29.09; H, 1.97.

Methyl-3-bromo-propiolate (83.7 g, 0.513 mol) is added to *N*-*t*-butyloxy-pyrrole (430 ml, 2.57 mol) under nitrogen. The dark mixture is warmed in a 90 °C bath for 30 h, is cooled, and the bulk of the excess *N*-*t*-butyloxy-pyrrole is removed *in vacuo* using a dry ice/acetone condenser. The dark oily residue is chromatographed over 1 kg silica gel (230-400 mesh) eluting with 0-15% EtOAc/hexane. The appropriate fractions are combined and concentrated to afford 97 g (57%) of 7-*tert*-butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate as a

30

dark yellow oil. HRMS (FAB) calc'd for $C_{13}H_{16}BrNO_4 + H$: 330.0341, found 330.0335 ($M+H$)⁺.

7-*tert*-Butyl 2-methyl 3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene-2,7-dicarboxylate (97 g, 0.294 mol) is added to 10% Pd/C (6.8g) in 900 ml absolute EtOH in a PARR bottle. The suspension is diluted with a solution of NaHCO₃ (25 g, 0.301 mol) in 250 ml water and the mixture is hydrogenated at 50 PSI for 2.5 h. The catalyst is removed by filtration, is washed with fresh EtOH, and the filtrate is concentrated *in vacuo* to give a residue. The residue is partitioned between 1 x 200 ml saturated NaHCO₃ and CH₂Cl₂ (4 x 100 ml). The combined organic layer is dried over 1:1 K₂CO₃/MgSO₄ and concentrated *in vacuo* to afford 72.8 g (98%) of (+/-) *endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate. MS (EI) for $C_{14}H_{22}O_4$, m/z : 255 (M)⁺.

(+/-)-*Endo*-7-*tert*-butyl 2-methyl 7-azabicyclo[2.2.1]heptane-2,7-dicarboxylate (72.8 g, 0.285 mol) is dissolved in 1000 ml dry MeOH in a dried flask under nitrogen. The solution is treated with solid NaOMe (38.5 g, 0.713 mol) neat, in a single lot and the reaction is warmed to reflux for 4h. The mixture is cooled to 0°C, is treated with 400 ml water, and the reaction is stirred 1h as it warms to RT. The mixture is concentrated *in vacuo* to about 400 ml and the pH of the aqueous residue is adjusted to 4.5 with 12N HCl. The precipitate is collected and dried. The tan, slightly tacky solid is washed with 2 x 100 ml 60% ether in hexane and is dried to provide 47 g (68%) of (+/-) *exo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid as an off-white powder. HRMS (FAB) calc'd for $C_{12}H_{19}NO_4 + H$: 242.1392, found 242.1390 ($M+H$)⁺.

(+/-)-*Exo*-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (103.9 g, 0.430 mol) is combined with TEA (60 ml, 0.430 mol) in 1200 ml dry toluene in a dry flask under nitrogen. The solution is treated drop-wise with diphenylphosphoryl azide (92.8 ml, 0.430 mol), and is allowed to stir for 20 min at RT. The mixture is treated with benzyl alcohol (47.9 ml, 0.463 mol), and the reaction is stirred overnight at 55°C. The mixture is cooled, is extracted successively with 2 x 500 ml 5% citric acid, 2 x 500 ml water, 2 x 500 ml saturated sodium bicarbonate, and 500 ml brine. The organic layer is dried over MgSO₄ and concentrated *in vacuo* to an amber oil. The crude material is chromatographed over 900 g silica gel (230-400 mesh), eluting with 10-30% EtOAc/hexane. The appropriate fractions are combined

and concentrated to give 106 g (71%) of (+/-) *exo-tert*-butyl 2-
 {[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate as a pale oil.
¹H NMR (CDCl₃) δ 1.29-1.60, 1.44, 1.62-2.01, 3.76-3.88, 4.10, 4.24, 5.10, 7.36 ppm.

(+/-) *Exo-tert*-Butyl 2-{[(benzyloxy)carbonyl]amino}-7-
 5 azabicyclo[2.2.1]heptane-7-carboxylate (1.5 g, 4.33 mmol) is combined with 10%
 Pd/C (150 mg) in 40 ml EtOH in a 250 ml Parr shaker bottle. The mixture is
 hydrogenated at 50 PSI for 1.5 h. The catalyst is removed by filtration and the filtrate
 is concentrated *in vacuo*. The crude material is chromatographed over 30 g silica gel
 (230-400 mesh), eluting with 7% MeOH/CH₂Cl₂ + 1% conc. NH₄OH. The
 10 appropriate fractions are combined and concentrated to provide 606 mg (66%) of
 (+/-) *exo-tert*-butyl 2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate. HRMS
 (FAB) calcd for C₁₁H₂₀N₂O₂+H: 213.1603, found 213.1580 (M+H)⁺. This racemic
 mixture will be referenced as (+/-)-7-aza-[2.2.1]-Amine.

Resolution of racemic carboxylate mixture:

15 The isolated (+/-) *exo-tert*-butyl 2-{[(benzyloxy)carbonyl]amino}-7-
 azabicyclo[2.2.1]heptane-7-carboxylate is resolved via preparative chiral HPLC
 (50x500 mm Chiralcel OJ column, 30 deg. C, 70 mL/min. 10/90 (v/v)
 isopropanol/heptane). The resolution affords 40 g of *tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-
 2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate and 42 g of
 20 *tert*-butyl-(1*R*, 2*S*, 4*S*)-(-)-2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-
 7-carboxylate.

The 2*R* enantiomer is triturated with 40 ml ether followed by 40 ml hexane (to
 remove lingering diastereo and enantiomeric impurities) and is dried to afford 30 g
 (56%) of purified *tert*-butyl (1*S*, 2*R*, 4*R*)-(+)-2{[(benzyloxy)carbonyl]amino}-7-
 25 azabicyclo[2.2.1]heptane-7-carboxylate with 99% enantiomeric excess. MS (EI) for
 C₁₉H₂₆N₂O₄, *m/z*: 346 (M)⁺. [α]_D²⁵ = 22, (c 0.42, chloroform).

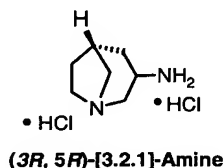
The 2*S* enantiomer is triturated with 40 ml ether followed by 40 ml hexane to
 give 35 g (66%) of purified *tert*-butyl (1*R*, 2*S*, 4*S*)-(-)-
 2{[(benzyloxy)carbonyl]amino}-7-azabicyclo[2.2.1]heptane-7-carboxylate with 99%
 30 enantiomeric excess. MS (EI) for C₁₉H₂₆N₂O₄, *m/z*: 346 (M)⁺. [α]_D²⁵ = -23, (c 0.39,
 chloroform).

tert-Butyl (1*S*, 2*R*, 4*R*)-(+)-2{[(benzyloxy)carbonyl]amino}-7-
 azabicyclo[2.2.1]heptane-7-carboxylate (9.5 g, 27.4 mmol) is combined with 950 mg

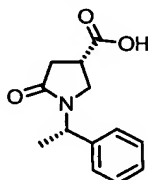
10% Pd/C in 75 ml absolute EtOH in a 500 ml Parr bottle. The reaction mixture is hydrogenated at 50 PSI for 3h, the catalyst is removed by filtration, and the filter cake is washed with MeOH. The filtrate is concentrated *in vacuo* to give 6.4 g of a residue. The crude material is chromatographed over 200 g silica gel (230-400 mesh) eluting with 7% CH₃OH/CHCl₃ containing 1% conc. NH₄OH. The appropriate fractions are combined and concentrated to give 5.61 g (96%) of *tert*-butyl-(1*S*, 2*R*, 4*R*)-(+)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate as a pale oil. MS (EI) for C₁₁H₂₀N₂O₂, *m/z*: 212 (M)⁺. [α]²⁵_D = 9, (*c* 0.67, CHCl₃). This will be referenced as (2*R*)-7-aza-[2.2.1]-Amine.

Preparation of 1-azabicyclo[3.2.1]octan-3-amine:

Preparation of the 3*R*,5*R*-[3.2.1]-Amine:

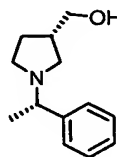


15 (3*S*)-1-[(*S*)-1-Phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid:

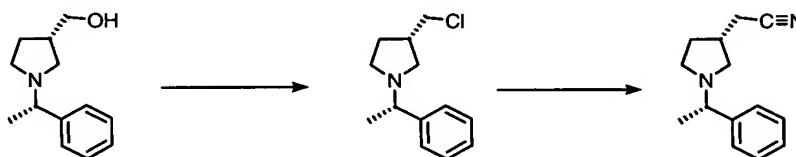


According to the literature procedure (Nielsen *et al.* J. Med. Chem **1990**, 70-77), a mixture of itaconic acid (123.17 g, 946.7 mmol) and (*S*)-(-)- α -methyl benzylamine (122.0 mL, 946.4 mmol) were heated (neat) in a 160°C oil bath for 4 h. Upon cooling, MeOH (~200 mL) was added and the resulting solid collected by filtration. The solid was treated with EtOH (~700 mL) and warmed using a steam bath until ~450 mL solvent remained. After cooling to rt, the solid was collected and dried to afford 83.2 g as a white crystalline solid: [α]²⁵_D = -80 (*c* 0.97, DMSO). MS (EI) *m/z* 233 (M⁺).

The lack of a resonance 3.59 indicates a single diastereomer. The other diastereomer can be retrieved from the initial MeOH tritulant. Attempts to crystallize this material generally led to small quantities of (3*RS*)-1-[(*S*)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid.

(3S)-1-[(S)-1-Phenethyl]-3-(hydroxymethyl)pyrrolidine:

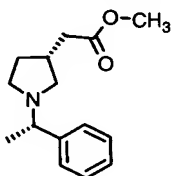
A suspension (3S)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidine-carboxylic acid (82.30 g, 352.8 mmol) in Et₂O (200 mL) was added in small portions to a slurry of LiAlH₄ (17.41 g, 458.6 mmol) in Et₂O (700 mL). The mixture began to reflux during the addition. The addition funnel containing the suspension was rinsed with Et₂O (2 x 50 mL), and the mixture was heated in a 50 °C oil bath for an additional 2 h and first allowed to cool to rt and then further cooled using an ice bath. The mixture was carefully treated with H₂O (62 mL). The resulting precipitate was filtered, rinsed with Et₂O, and discarded. The filtrate was concentrated to a yellow oil. When EtOAc was added to the oil, a solid began to form. Hexane was then added and removed by filtration and dried to afford 43.3 g as a white solid. $[\alpha]_D^{25} = -71$ (c 0.94, CHCl₃). MS (EI) *m/z* 205 (M⁺).

(3R)-1-[(S)-1-Phenethyl]-3-(cyanomethyl)pyrrolidine:

A solution of (3S)-1-[(S)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine (42.75 g, 208.23 mmol) in chloroform (350 mL) was heated to reflux under N₂. The solution was treated with a solution of thionyl chloride (41.8 mL, 573 mmol) in chloroform (40 mL) dropwise over 45 min. The mixture stirred for an additional 30 min, was cooled and concentrated. The residue was diluted with H₂O (~200 mL), 1 N NaOH was added until a pH ~ 8 (pH paper). A small portion (~50 mL) of sat. NaHCO₃ was added and the basic mixture was extracted with EtOAc (3 x 400 mL), washed with brine, dried over MgSO₄, filtered and concentrated to give 46.51 g of a red-orange oil for (3S)-1-[(S)-1-phenethyl]-3-(chloromethyl)pyrrolidine: *R_f*: 0.50 (EtOAc-hexane 1:1); MS (ESI⁺) *m/z* 224.2 (MH⁺). The chloride (46.35 g, 208.0 mmol) was transferred to a flask, dimethyl sulfoxide (200 mL) was added, and the solution was

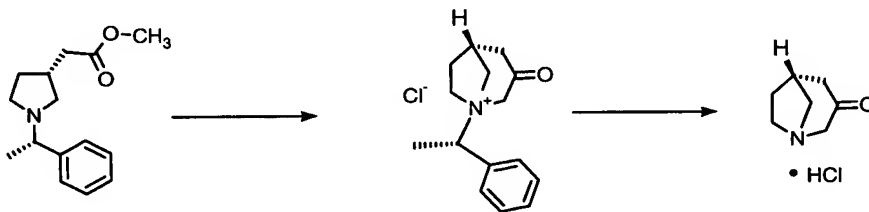
treated with NaCN (17.84 g, 363.9 mmol). The mixture was heated under N₂ in a 100°C oil bath overnight and was cooled. The brown mixture was poured into H₂O (300 mL) and extracted with EtOAc (1000 mL in portions). The combined organic layer was washed with H₂O (6 x ~50 mL), brine (~100 mL), dried (MgSO₄), filtered and concentrated to give 40.61 g as an orange-red oil: R_f: 0.40 (EtOAc-PhCH₃ 1:1). MS (ESI+) for *m/z* 215.2 (M+H⁺).

(3R)-Methyl 1-[(S)-1-phenylethyl]pyrrolidine-3-acetate:



Acetyl chloride (270 mL, 3.8 mol) was carefully added to a flask containing chilled (0°C) methanol (1100 mL). After the addition was complete, the acidic solution stirred for 45 min (0 °C) and then (3R)-1-[(S)-1-phenethyl]-3-(cyanomethyl)pyrrolidine (40.50 g, 189.0 mmol) in methanol (200 mL) was added. The ice bath was removed and the mixture stirred for 100 h at rt. The resulting suspension was concentrated. Water (~600 mL) was added, the mixture stirred for 45 min and then the pH was adjusted (made basic) through the addition of ~700 mL sat. aq. NaHCO₃. The mixture was extracted with EtOAc (3 x 300 mL). The combined organics were washed with brine, dried (MgSO₄), filtered through celite and concentrated to give 36.86 g as an orange-red oil. MS (ESI+) *m/z* 248.2 (M+H⁺).

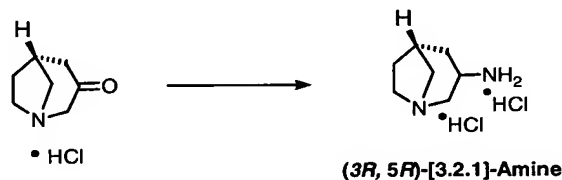
(5R)-1-Azabicyclo[3.2.1]octan-3-one hydrochloride:



A solution of (3R)-methyl 1-[(S)-1-phenylethyl]pyrrolidine-3-acetate (25.72g, 104.0 mmol) in THF (265 mL) was cooled under N₂ in a CO₂/acetone bath. Next, ICH₂Cl (22.7 mL, 312.0 mmol) was added, and the mixture stirred for 30 min. A solution of 2.0M lithium diisopropylamide (heptane/THF/ethylbenzene, 156 mL, 312 mmol) was added slowly over 30 min. The internal temperature reached a maximum

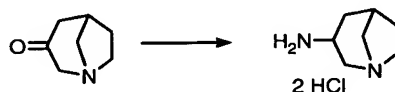
of -40°C during this addition. After 1 h, sat. NH_4Cl (100 mL) was added and the mixture was allowed to warm to rt. The organic layer was separated, dried (MgSO_4), filtered and concentrated. The resulting red-brown foam was chromatographed (300 g SiO_2 , CHCl_3 - MeOH - NH_4OH (89:10:1) followed by CHCl_3 - MeOH (3:1). The product fractions were pooled and concentrated to afford (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride (10.12g) as a tan foam (MS (ESI+) m/z 230.1 ($\text{M}+\text{H}^+$)). This foam (10.1 g, 38 mmol) was taken up in MeOH (500 mL), 10% $\text{Pd}(\text{C})$ (3.0 g) added and the mixture was hydrogenated (45 psi) overnight. The mixture was filtered and re-subjected to the reduction conditions (9.1 g, 10% Pd/C , 50 psi). After 5 h, TLC indicated the consumption of the (5*R*)-3-oxo-1-[(1*S*)-1-phenylethyl]-1-azoniabicyclo[3.2.1]octane chloride. The mixture was filtered, concentrated and triturated (minimal *i*PrOH) to give 3.73 g in two crops, as an off-white solid: $[\alpha]_{\text{D}}^{25} = 33$ (c 0.97, DMSO). MS (EI) m/z 125 (M^+).

(3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride:



To a flask containing (5*R*)-1-azabicyclo[3.2.1]octan-3-one hydrochloride (3.64 g, 22.6 mmol), hydroxylamine hydrochloride (2.04 g, 29.4 mmol), and ethanol (130 mL) was added sodium acetate trihydrate (9.23 g, 67.8 mmol). The mixture stirred for 3 h and was filtered and concentrated. The resulting white solid was taken up in *n*-propanol (100 mL) and sodium (~13.6 g, 618 mmol) was added over 20-25 portions. The reaction spontaneously began to reflux, and the reaction was heated in an oil bath (100°C). The addition was complete in ~20 min and the mixture had solidified after ~40 min. The oil bath was removed and *n*-propanol (2 x 25 mL) was added dissolving the remaining sodium metal. The mixture was carefully quenched through the dropwise addition of H_2O (100 mL). Saturated aq. NaCl (20 mL) was added, and the layers were separated. The organic layer was dried (MgSO_4), filtered, treated with freshly prepared MeOH/HCl , and concentrated. The resulting solid was triturated with 30 mL EtOH , filtered and dried *in vacuo* to afford 3.51 g as a white solid: $[\alpha]_{\text{D}}^{25} = -3$ (c 0.94, DMSO). MS (FAB) m/z 127 (MH^+).

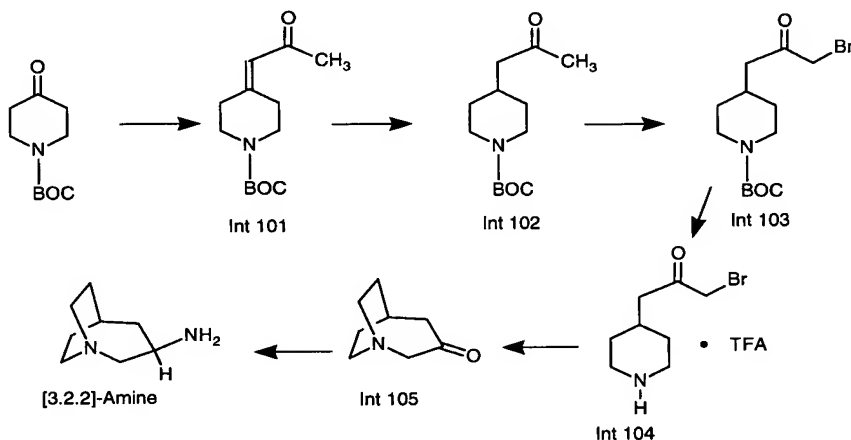
Preparation of *endo*-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride (*endo*-[3.2.1]-Amine):



5 A mixture of 1-azabicyclo[3.2.1]octan-3-one hydrochloride (2.80 g, 17.3 mmol), ethanol (25 mL), and hydroxylamine hydrochloride (1.56 g, 22.4 mmol) is treated with sodium acetate trihydrate (7.07 g, 51.2 mmol). The mixture is stirred for 3 h and evaporated *in vacuo*. The residue is diluted with CH₂Cl₂, treated with charcoal, filtered and evaporated. The resulting oxime (3.1 mmol) is treated with
 10 acetic acid (30 mL) and hydrogenated at 50 psi over PtO₂ (50 mg) for 12 h. The mixture is then filtered and evaporated. The residue is taken up in a minimal amount of water (6 mL) and the pH is adjusted to >12 using solid NaOH. The mixture is then extracted with ethyl acetate (4 X 25 mL), dried over MgSO₄, filtered, treated with ethereal HCl, and evaporated to give the give *endo*-[3.2.1]-Amine.

15

Preparation of the 3.2.2 Amines:



Preparation of *tert*-butyl 4-(2-oxopropylidene)piperidine-1-carboxylate (Int 101):

20 Sodium hydride (60% oil dispersion, 2.01 g, 50.2 mmol) is washed with pentane (3X) and suspended in dry THF (40 mL). The solution is cooled to 0°C before diethyl (2-oxopropyl)phosphonate (9.75 g, 50.2 mmol) is added dropwise. After complete addition, the solution is warmed to rt and stirred for 30 min. *tert*-Butyl 4-oxo-1-piperidinecarboxylate (5.0g, 25.1 mmol) is added in portions over 10

min, followed by stirring at rt for 2 h. A saturated aqueous solution of ammonium chloride is added, followed by dilution with ether. The organic layer is extracted with water. The organic layer is dried over anhydrous MgSO_4 , filtered and concentrated to a yellow oil. The crude product is purified by flash chromatography on silica gel.

- 5 Elution with hexanes-ether (60:40) gave 4.5 g (75%) of Int 101 as a white solid: ^1H NMR (CDCl_3) δ 6.2, 3.5, 3.4, 2.9, 2.3, 2.2, 1.5.

Preparation of *tert*-butyl 4-(2-oxopropyl)piperidine-1-carboxylate (Int 102):

- 10 A mixture of Int 101 (4.5 g, 19 mmol) and 10% palladium on activated carbon (450mg) in EtOH (150 mL) is placed in a Parr bottle and hydrogenated for 5 h at 50 psi. The mixture is filtered through Celite, and the filtrate is concentrated *in vacuo* to afford 4.3 g (94%) of Int 102 as a clear oil: ^1H NMR (CDCl_3) δ 4.1, 2.8, 2.4, 2.2, 2.0, 1.7, 1.5, 1.1.

- 15 Preparation of *tert*-butyl 4-(3-bromo-2-oxopropyl)piperidine-1-carboxylate (Int 103):

- To a stirred solution lithium hexamethyldisilylamide in THF (20.0 mL, 1.0 M) in a -78°C bath is added chlorotrimethylsilane (11.0 mL, 86.4 mmol) dropwise. The mixture is stirred at -78°C for 20 min, followed by addition of Int 102 (3.21 g, 13.3 mmol) in a solution of THF (50 mL) dropwise. After complete addition, the mixture is stirred at -78°C for 30 min. The mixture is warmed to 0°C in an ice-water bath and phenyltrimethylammonium tribromide (5.25 g, 14.0 mmol) is added. The mixture is stirred in an ice-bath for 30 min, followed by the addition of water and ether. The aqueous layer is washed with ether, and the combined organic layers are washed with saturated aqueous sodium thiosulfate solution. The organic layer is dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* to afford a yellow oil. The crude product is purified by flash chromatography on silica gel. Elution with hexanes-ether (60:40) gave 2.2 g (52%) of Int 103 as a lt. yellow oil: ^1H NMR (CDCl_3) δ 4.2-4.1, 3.9, 2.8, 2.7, 2.6, 2.1-2.0, 1.7, 1.5, 1.2-1.1.2.

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Preparation of 1-bromo-3-piperidin-4-ylacetone trifluoroacetate (Int 104):

To a stirred solution of Int 103 (2.2 g, 6.9 mmol) in CH_2Cl_2 (30 mL) in an ice-water bath is added trifluoroacetic acid (10 mL, 130 mmol). The mixture is stirred at

0°C for 30 min. The volatiles are removed *in vacuo* to afford 2.0 g (87%) of Int 104 as a yellow residue: MS (ESI) for C₈H₁₅BrNO [M+H] *m/e* 220.

Preparation of 1-azabicyclo[3.2.2]nonan-3-one (Int 105):

5 To a stirred solution of DIEA (13 mL) in acetonitrile (680 mL) at reflux temperature is added a solution of Int 104 (2.0 g, 6.0 mmol) in acetonitrile (125 mL) over a 4 h period via syringe pump. The mixture is kept at reflux temperature overnight. The mixture is concentrated *in vacuo* and the remaining residue is partitioned between a saturated aqueous potassium carbonate solution and CHCl₃-
10 MeOH (90:10). The aqueous layer is extracted with CHCl₃-MeOH (90:10), and the combined organic layers are dried over MgSO₄, filtered and concentrated *in vacuo* to a brown oil. The crude product is purified by flash chromatography on silica gel. Elution with CHCl₃-MeOH-NH₄OH (95:4.5:0.5) gives 600 mg (72%) of Int 105 as a clear solid: ¹H NMR (CDCl₃) δ 3.7, 3.3-3.2, 3.1-3.0, 2.7, 2.3, 2.0-1.8.

15

Preparation of 1-azabicyclo[3.2.2]nonan-3-amine bis(4-methylbenzenesulfonate) ([3.2.2]-Amine):

To a stirred mixture of Int 105 (330 mg, 2.4 mmol) and sodium acetate•trihydrate (670 mg, 4.8 mmol) in EtOH (6.0 mL) is added
20 hydroxylamine•hydrochloride (200 mg, 2.8 mmol). The mixture is stirred at rt for 10 h. The mixture is filtered and the filtrate is concentrated *in vacuo* to a yellow solid. To a solution of the solid (350 mg, 2.3 mmol) in *n*-propanol (30 mL) at reflux temperature is added sodium metal (2.0 g, 87 mmol) in small portions over 30 min. Heating at reflux is continued for 2 h. The solution is cooled to rt and brine is added.
25 The mixture is extracted with *n*-propanol, and the combined organic layers are concentrated *in vacuo*. The residue is taken up in CHCl₃ and the remaining solids are filtered. The filtrate is dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to a clear solid. To a stirred solution of the solid (320 mg, 2.3 mmol) in EtOH (4 mL) is added *p*-toluenesulfonic acid monohydrate (875 mg, 4.6 mmol). The
30 solution is warmed in a water bath to 45°C for 30 min, followed by concentration of the solvent to afford 710 mg (62%) of [3.2.2]-Amine as a white solid: ¹H NMR (CD₃OD) δ 7.7, 7.3, 4.1-3.9, 3.6-3.4, 2.6-2.5, 2.4, 2.2-2.1, 2.1-2.0, 1.9.

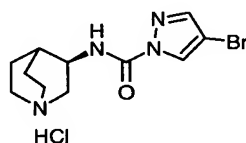
Resolution of stereoisomers:

The amine can be coupled to form the appropriate amides or thioamides as a racemic mixture. The racemic mixture can then be resolved by chromatography using chiral columns or chiral HPLC, techniques widely known in the art, to provide the requisite resolved enantiomers 3(*R*) and 3(*S*) of said amides.

COUPLINGS

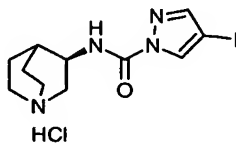
The following examples are provided as examples and are not intended to limit the scope of this invention to only those provided examples and named compounds. Also, the salts made in the examples are only exemplary and are not intended to limit the invention. Any pharmaceutically acceptable salt can be made by one of ordinary skill in the art. Further, the naming of specific stereoisomers is for exemplification, and is not intended to limit in anyway the scope of the invention. The invention includes the following examples in pure stereoisomeric form or as racemic mixtures.

Example 1: N-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-4-bromo-1*H*-pyrazole-1-carboxamide hydrochloride:



A solution of 4-bromopyrazole (0.52g, 3.5mmol) in 30mL EtOAc is added to excess phosgene (10mL, 20% solution in toluene) in EtOAc. After complete addition, the solution is refluxed for 1 h, cooled and concentrated *in vacuo*. EtOAc is added, and the mixture is concentrated again. The residue is treated with 20mL THF, (*R*)-(+)-3-aminoquinuclidine dihydrochloride (0.71g, 3.5mmol) and excess TEA (5.0mL, 68.1mmol). After 60h, 1N NaOH solution is added. The mixture is extracted with CHCl₃, dried (MgSO₄), filtered and concentrated. The residue is purified by flash chromatography (Biotage 40S, 90:9:1 CHCl₃/MeOH/NH₄OH). The hydrochloride salt is prepared and recrystallized from MeOH/EtOAc to afford 289 mg (25%) of a white solid. HRMS (FAB) calcd for C₁₁H₁₅BrN₄O+H 299.0508, found 299.0516.

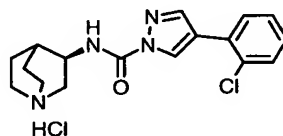
Example 2: N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-iodo-1H-pyrazole-1-carboxamide hydrochloride:



Phenyl chloroformate (0.75mL, 6.0mmol) is added dropwise to a solution of 4-iodopyrazole (1.05g, 5.4mmol) and triethylamine (0.9mL, 6.5mmol) in 15mL CH₂Cl₂. The reaction is stirred at RT. After 60h, water is added. The mixture is extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated. Hexane is added and the solvent is removed *in vacuo*. A white solid forms on standing to provide 1.6g (95%) of phenyl 4-iodo-1H-pyrazole-1-carboxylate. MS (EI) *m/z* 315.1 (M⁺).

Phenyl 4-iodo-1H-pyrazole-1-carboxylate (1.6g, 5.2mmol) and (R)-(+)-3-aminoquinuclidine dihydrochloride (1.0g, 5.2mmol) are suspended in 10mL DMF. DIEA (2.7mL, 15.5mmol) is added dropwise. After 36 h, the solvent is removed and the residue is taken up in 1N NaOH and CHCl₃. The aqueous layer is extracted with CHCl₃, dried (MgSO₄), filtered and concentrated. The residue is purified by chromatography (Biotage 40S, 90:9:1 CHCl₃/MeOH/NH₄OH) to provide 1.66g (93%) of the product as a white solid. A portion of the material is converted into the hydrochloride salt and recrystallized from MeOH/EtOAc. HRMS (FAB) calcd for C₁₁H₁₅IN₄O+H 347.0370, found 347.0357.

Example 3: N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(2-chlorophenyl)-1H-pyrazole-1-carboxamide hydrochloride:



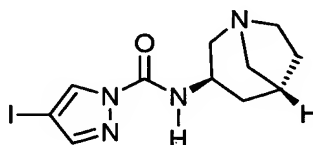
Hydrazine hydrate (0.55mL, 11.3mmol) is added to a suspension of 2-chlorophenylmalondialdehyde dissolved in 20mL EtOH. The mixture is heated under reflux for 3min, then allowed to stir at RT overnight. The solvent is removed *in vacuo* to provide 4-(2-chlorophenyl)-1H-pyrazole as a yellow solid. MS (EI) *m/z* 177.0 (M⁺).

4-Nitrophenyl chloroformate (2.3g, 11.5mmol) and 4-(2-chlorophenyl)-1H-pyrazole (2.0g, 11.0mmol) are dissolved in 30mL CH₂Cl₂ and cooled to 0°C. TEA

(1.7mL, 12.0mmol) is added, and the reaction is allowed to warm to RT. After 30 min, additional 4-nitrophenyl chloroformate (0.25g) and TEA are added. After 1h, water is added. The mixture is extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated to give a solid. The solid is triturated with hexanes, filtered and dried to provide 1.7g (45%) of the crude 4-nitrophenyl 4-(2-chlorophenyl)-1H-pyrazole-1-carboxylate.

A portion of 4-nitrophenyl 4-(2-chlorophenyl)-1H-pyrazole-1-carboxylate (0.34g, 1.0mmol) and (R)-(+)-3-aminoquinuclidine dihydrochloride (0.22g, 1.1mmol) are suspended in 5mL DMF. TEA (0.4mL, 3.0mmol) is added dropwise. After 18 h, 1N NaOH is added, and the solvent is removed under reduced pressure. The residue is taken up in 1N NaOH and CHCl₃. The aqueous layer is extracted with CHCl₃, dried (MgSO₄), filtered and concentrated. The residue is purified by chromatography (Biotage 40S, 90:9:1 CHCl₃/MeOH/NH₄OH). The hydrochloride salt is prepared and recrystallized from MeOH/EtOAc to provide 102 mg (28%) of the product. HRMS (FAB) calcd for C₁₇H₁₉ClN₄O+H 331.1325, found 331.1312.

Example 4: *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]-4-iodo-1H-pyrazole-1-carboxamide:



A solution of 4-iodopyrazole (1.05 g, 5.4 mmol) in 15 mL CH₂Cl₂ is treated with triethyl amine (0.90 mL, 6.5 mmol) and phenylchloroformate (0.75 mL, 6.0 mmol). The mixture is stirred for 5h and treated with H₂O (1 mL). The aqueous layer is discarded and the organic dried (MgSO₄). The mixture is filtered, and evaporated to a yellow oil which solidifies upon evaporation from hexane. A portion of this solid (0.628 g, 2.0 mmol) is added to DMF (10 mL) containing (3*R*,5*R*)-1-azabicyclo[3.2.1]octan-3-amine dihydrochloride (0.398 g, 2.0 mmol). Diisopropylethyl amine (1.1 mL, 6.0 mmol) is added and the mixture becomes nearly homogeneous. The mixture is extracted between EtOAc and H₂O. The organic layer is washed with H₂O (3X), brine, dried (MgSO₄), and the mixture is evaporated. The resulting material is taken up in hot EtOAc, filtered through celite, and allowed to stand at RT. The resulting solid is collected and dried to afford Example 4 (0.142 g,

20 %) as a white solid: HRMS (ESI) calcd for $C_{11}H_{15}N_4OI$ (MH⁺) 347.0370, found 347.0370. Anal. Calcd for $C_{11}H_{15}IN_4O$: C, 38.17; H, 4.37; N, 16.18. Found: C, 38.43; H, 4.42; N, 16.11.

The acids are coupled with the other amines identified herein using the
5 coupling methods described herein to make examples with the acids and corresponding amines.

Materials and Methods for Determining $\alpha 7$ nAChR Agonist Activity

10 **Cell-based Assay for Measuring the EC_{50} of $\alpha 7$ nAChR Agonists**

Construction and expression of the $\alpha 7$ -5HT₃ receptor:

The cDNA encoding the N-terminal 201 amino acids from the human $\alpha 7$ nAChR that contain the ligand binding domain of the ion channel was fused to the
15 cDNA encoding the pore forming region of the mouse 5HT₃ receptor as described by Eisele JL, et al., Chimaeric nicotinic-serotonergic receptor combines distinct ligand binding and channel specificities, Nature (1993), Dec. 2;366(6454):479-83, and modified by Groppi, et al., WO 00/73431. The chimeric $\alpha 7$ -5HT₃ ion channel was inserted into pGS175 and pGS179 which contain the resistance genes for G-418 and
20 hygromycin B, respectively. Both plasmids were simultaneously transfected into SH-EP1 cells and cell lines were selected that were resistant to both G-418 and hygromycin B. Cell lines expressing the chimeric ion channel were identified by their ability to bind fluorescent α -bungarotoxin on their cell surface. The cells with the highest amount of fluorescent α -bungarotoxin binding were isolated using a
25 Fluorescent Activated Cell Sorter (FACS). Cell lines that stably expressed the chimeric $\alpha 7$ -5HT₃ were identified by measuring fluorescent α -bungarotoxin binding after growing the cells in minimal essential medium containing nonessential amino acids supplemented with 10% fetal bovine serum, L-glutamine, 100 units/ml penicillin/streptomycin, 250 ng/ml fungizone, 400 μ g/ml hygromycin B, and 400
30 μ g/ml G-418 at 37° C with 6% CO₂ in a standard mammalian cell incubator for at least 4 weeks in continuous culture.

Assay of the activity of the chimeric $\alpha 7$ -5HT₃ receptor

To assay the activity of the $\alpha 7$ -5HT₃ ion channel, cells expressing the channel were plated into each well of either a 96 or 384 well dish (Corning #3614) and grown to confluence prior to assay. On the day of the assay, the cells were loaded with a 1:1 mixture of 2 mM Calcium Green 1, AM (Molecular Probes) dissolved in anhydrous DMSO and 20% pluronic F-127 (Molecular Probes). This solution was added directly to the growth media of each well to achieve a final concentration 2 μ M. The cells were incubated with the dye for 60 min at 37° C and then washed with a modified version of Earle's balanced salt solution (MMEBSS) as described in WO 00/73431. The ion conditions of the MMEBSS was adjusted to maximize the flux of calcium ion through the chimeric $\alpha 7$ -5HT₃ ion channel as described in WO 00/73431. The activity of compounds on the chimeric $\alpha 7$ -5HT₃ ion channel was analyzed on FLIPR. The instrument was set up with an excitation wavelength of 488 nanometers using 500 milliwatts of power. Fluorescent emission was measured above 525 nanometers with an appropriate F-stop to maintain a maximal signal to noise ratio. Agonist activity of each compound was measured by directly adding the compound to cells expressing the chimeric $\alpha 7$ -5HT₃ ion channel and measuring the resulting increase in intracellular calcium that is caused by the agonist-induced activation of the chimeric ion channel. The assay is quantitative such that concentration-dependent increase in intracellular calcium is measured as concentration-dependent change in Calcium Green fluorescence. The effective concentration needed for a compound to cause a 50% maximal increase in intracellular calcium is termed the EC₅₀. The examples of the present invention have EC₅₀ values between 171nM and 366nM.

Binding Constants:

Another way for measuring $\alpha 7$ nAChR agonist activity is to determine binding constants of a potential agonist in a competition binding assay. For $\alpha 7$ nAChR agonists, there is good correlation between functional EC₅₀ values using the chimeric $\alpha 7$ -5HT₃ ion channel as a drug target and binding affinity of compounds to the endogenous $\alpha 7$ nAChR.

Membrane Preparation.

Male Sprague-Dawley rats (300-350g) are sacrificed by decapitation and the brains (whole brain minus cerebellum) are dissected quickly, weighed and

homogenized in 9 volumes/g wet weight of ice-cold 0.32 M sucrose using a rotating pestle on setting 50 (10 up and down strokes). The homogenate is centrifuged at 1,000 x g for 10 minutes at 4 °C. The supernatant is collected and centrifuged at 20,000 x g for 20 minutes at 4 °C. The resulting pellet is resuspended to a protein concentration of 1 - 8 mg/mL. Aliquots of 5 mL homogenate are frozen at -80 °C until needed for the assay. On the day of the assay, aliquots are thawed at rt and diluted with Kreb's - 20 mM Hepes buffer pH 7.0 (at rt) containing 4.16 mM NaHCO₃, 0.44 mM KH₂PO₄, 127 mM NaCl, 5.36 mM KCl, 1.26 mM CaCl₂, and 0.98 mM MgCl₂, so that 25 - 150 µg protein are added per test tube. Proteins are determined by the Bradford method (Bradford, M.M., *Anal. Biochem.*, 72, 248-254, 1976) using bovine serum albumin as the standard.

Binding Assay.

For saturation studies, 0.4 mL homogenate are added to test tubes containing buffer and various concentrations of radioligand, and are incubated in a final volume of 0.5 mL for 1 hour at 25 °C. Nonspecific binding was determined in tissues incubated in parallel in the presence of 0.05 mls MLA for a final concentration of 1 µM, added before the radioligand. In competition studies, drugs are added in increasing concentrations to the test tubes before addition of 0.05 mls [³H]-MLA for a final concentration 3.0 to 4.0 nM. The incubations are terminated by rapid vacuum filtration through Whatman GF/B glass filter paper mounted on a 48 well Brandel cell harvester. Filters are pre-soaked in 50 mM Tris HCl pH 7.0 - 0.05 % polyethylenimine. The filters are rapidly washed two times with 5 mL aliquots of cold 0.9% saline and then counted for radioactivity by liquid scintillation spectrometry.

Data Analysis.

In competition binding studies, the inhibition constant (K_i) was calculated from the concentration dependent inhibition of [³H]-MLA binding obtained from non-linear regression fitting program according to the Cheng-Prusoff equation (Cheng, Y.C. and Prusoff, W.H., *Biochem. Pharmacol.*, 22, p. 3099-3108, 1973). Hill coefficients were obtained using non-linear regression (GraphPad Prism sigmoidal dose-response with variable slope).